EXHIBIT 1

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

IN RE: ZOLOFT (SERTRALINE HYDROCHLORIDE) PRODUCTS LIABILITY LITIGATION	:	**MDL No. 2342**
	:	**2:12-md-02342-CMR**
	:	**HON. CYNTHIA M. RUFE**

Expert Report
Michael Levin, Ph.D
June 15, 2015

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I was asked during my Daubert testimony if there were any data that I was aware of that would demonstrate and support my opinions in *mammalian or human models.* This short report answers these questions.

I. Qualifications

By way of review and to provide an update to my professional experiences, I am a Professor in the Department of Biology at Tufts University, holding the endowed Vannevar Bush Chair, and serving as director of the Tufts Center for Regenerative and Developmental Biology. I also have an adjunct appointment at Harvard's Wyss Institute. I have worked in this field for decades and have devoted my career to the study of mechanisms that pattern the embryonic body. I received a Ph.D. from Harvard School of Medicine, specifically for my identification of the genetic mechanisms that dictate the positioning of the heart and visceral organs (an issue of key relevance to the effects of Zoloft and similar drugs). My work [1], was the first research that explained the molecular mechanisms driving consistent left-right asymmetry in the placement of the heart and other organs, and the journal *Nature* listed this discovery as "one of the milestones in developmental biology of the last century".

Throughout my post-doctoral training and my independent career at Forsyth Institute (affiliate of Harvard School of Dental Medicine), my laboratory has worked on identifying novel mechanisms of embryonic patterning, with a specific focus on the role of serotonin and voltage gradients in this process; I was the first scientist to study the role of serotonin and ion channel activity in embryonic laterality. I founded the Forsyth Center for Regenerative and Developmental Biology, and became Full Professor in 2007. I have received a number of awards for our work on molecular mechanisms of development and birth defects, including the Scientist of Vision award, and the Distinguished Scholar award, as well as the Established Investigator Award from the American Heart Association for my work on the role of serotonin in cardiac laterality. I also have extensive specific expertise in the developmental roles of ion channel activity; for example, my recent paper in the Journal of Neuroscience showed how genetic brain defects can be repaired (despite the presence of DNA mutations in key brain patterning genes) by manipulation of ion channel activity. Thus, my lab is a world leader in the discovery of mechanisms by which ion channels in non-neural cells control organ development – this is also a key aspect of understanding the ways in which Zoloft can affect embryogenesis of a number of important body systems. Many of our grant awards are specifically to fund my work on the role that ion channels play in developmental patterning; these funding sources support my work because they understand that basic research on ionic and serotonergic work in non-mammalian and mammalian systems are very relevant for human medicine.

I am an expert in molecular developmental biology, having authored over 140 peer-reviewed published papers on patterning mechanisms (including numerous papers on serotonin signaling, in which we routinely use serotonin reuptake inhibitors to study embryonic development and cellular function in vertebrate animal models, and on ion channels, in which we often use drugs that regulate ion channel activity to modulate the growth and form of brain, face, heart, and appendages). My collaborators and others have used my methods and results to advance their own work in human tissues and mouse embryogenesis. My papers have been published in top-tier journals including *Cell, Nature, Proceedings of the Academy of Sciences of the U.S.A., Journal of Neuroscience,* and *Development*.

Our work at the forefront of developmental bioelectricity, molecular genetics of development, use of ion channels to drive regeneration and repair birth defects, and development of the first artificial intelligence platform for discovering mechanistic explanations of patterning malformations has garnered wide coverage from top press outlets, including *Science*, *Nature*, *New Scientist*, *Boston Globe*, *Forbes*, *New York Times*, *Newsweek*, *Scientific American*, *and Physics World:*

- A Computer Just Solved This 100-Year-Old Biology Problem (Popular Mechanics, June 2015)
- Computer independently solves 120-year-old biological mystery (Wired, June 2015)
- Electrical zap of cells shapes growing brains (*Science News*, March 2015)
- Bioelectrical Signals Can Stunt or Grow Brain Tissue (*Scientific American*, March 11, 2015)
- Bioelectric signals spark brain growth (*Nature*, March 11, 2015)
- Tadpole eye transplant shows new way to grow nerves (*Science News*, December 2, 2014)
- Mapping The Body's Wiring For Medical Breakthroughs (*Newsweek*, August 7, 2014)
- Cracking the code to regrow human limbs (*New Scientist*, June 2, 2014)
- Could this man hold the secret to human regeneration? (*Medium*, January 2014)
- An electrical misunderstanding (*Physics World*, 2013)
- It's Electric: Biologists Seek to Crack Cell's Bioelectric Code (*Scientific American*, Mar. 27, 2013)
- Bioelectric signaling controls tissue shape and structure (*PhysicsToday*, March 2013)
- Tadpoles "see" with Eyes on Their Tails in Tufts Experiment (Feb-March 2013)
    - Boston.com
    - Science on NBC News
    - TheScientist
    - Science
    - The Boston Globe
    - ABC News
- Electric Shock (*Read Matter*, Dec. 2012)
- Meet Michael Levin, PhD. (*Science for the Public*)
- Building the Body Electric (*Science News*, Dec. 31, 2011)
- Researchers Discover that Changes in Bioelectric Signals can Trigger Organ Growth (Dec. 8, 2011)
    - Forbes
    - Science News
    - PhysOrg
- My, Your Eyes Are So Electric (*Science*, Dec. 7, 2011)
- Lessons on Regrowth, on a Small Scale (*The Boston Globe*, Jan. 3, 2011)
- An Electrical Switch for Cancer? (*The Scientist*, Oct. 19, 2010)
- Salt Infusion Could be a Remedy for Damaged Cells (Oct. 2010)
    - A Salty Tail
    - New York Times
- Recipes for Limb Renewal (*Chemical and Engineering News*, Aug. 2, 2010)
- Electricity Sparks Stem-Cell Transformation (*New Scientist*, Dec. 2008)
- Spark of Life: Electricity and Regeneration (*Science*, Sept. 2007)

- Electricity can spark limb regeneration (Feb. 28, 2007)
  - Nature
  - The Scientist

Because I am a recognized expert in these areas, I am routinely sent manuscripts for my evaluation from all the major developmental biology and biomedicine journals, having received a "Frequent Reviewer" mention from journals like *Nature*. I also review grants for the National Institute of Health, the National Science Foundation, and many private funders in the U.S. and around the world. My group receives funding from the American Heart Association, National Institutes of Health, National Science Foundation, Department of Defense (DARPA), March of Dimes, W. M. Keck Foundation, and other sources. In addition to our very active primary research program, I teach students at the graduate and undergraduate level (focusing on topics of molecular mechanisms of embryogenesis and pharmacological modulation thereof), and mentor post-doctoral candidates in my lab (who then go on to become independent assistant professors at other institutions).

Attached as Appendix 1 is my Curriculum Vitae for a more complete narration of my qualifications and expertise. A summary of my testimony as an expert witness in the last four years is attached at Appendix 2.

II. Methodology

I have relied upon my knowledge and experience in the field of molecular biology, which includes my own studies with SSRIs and their impact on embryonic development. This knowledge and experience is based on my training and years of experience conducting mechanistic testing in many animal models. In formulating my opinions, I have reviewed and analyzed hundreds of peer-reviewed papers, which include many on which I served as an author. I arrived at my opinions in this case no differently than I do in my lab when tasked with a scientific question, such as I the one which I was asked herein. I consider the developmental process in question, study the state-of-the-art literature on the molecular components that are known to be involved in this developmental process, analyze the different ways this process can be perturbed, critically evaluate the available studies on the downstream targets and molecular mechanism of action of the compound in question, and rigorously consider whether and how the compound (in this case Zoloft and SSRIs) is or is not likely to interfere with the mechanisms involved in embryogenesis, and if so, how. I have read the literature, including papers on cell biology, developmental genetics, pharmacology/toxicology, etc., to formulate the best possible answer. Many of my opinions regarding developmental malformations induced by ion channel and serotonergic signal disruption by reagents such as SSRIs have been scrutinized by the peer-review process and are published in some of the top scientific journals in the world.

My opinions in this report are expressed within a reasonable degree of scientific certainty and are based upon my education, training, experience and specialized knowledge in the field of molecular biology specifically studying the mechanistic role that serotonin and ion channel play in normal embryogenesis, as well as the role SSRIs have in perturbing normal development and cell functions across the animal kingdom.

All of my opinions are based upon methodologies and materials which are generally accepted and reasonably relied upon by experts in the field of molecular biologist studying these same principles, as well as other scientific disciplines, including many peer-reviewed papers in research journals. In forming these opinions, I have relied upon the information and data available at the time these opinions were rendered, but focused on new data since the April 2014 Daubert Hearing in this matter. A list of the documents I have recently reviewed and considered attendant to this report are listed on my Reference List, attached as Appendix 3.

III. Summary of Opinions

1. Serotonin plays a crucial role in embryogenesis, which includes left-right (laterality) patterning in mammals and humans.
2. Ion channels are also centrally involved in embryogenesis in mammal and humans.
3. SSRIs including Zoloft can and do perturb serotonin signaling and ion channel functioning, resulting in teratogenesis. Thus, SSRIs are capable of causing cardiac birth defects from a mechanistic standpoint.
4. Data, including peer-reviewed studies, support these mechanisms of teratogenicity in mammalian and human models.

This report is a discussion of new data, which strongly support my original Daubert opinion, including: presence of serotonin and its transporter in early rabbit embryos (strengthening the relevance of my mechanism opinions to mammals), publication of a paper showing that human patients with randomization of the organs have ion channel mutations, in some of the same ion channels targeted by Zoloft (providing a clear evidence of my ion channel mechanism for impact of Zoloft on human laterality), and publication of several papers showing craniofacial defects due to ion channel mutations (clearly showing that my ion channel teratogenesis mechanism is directly relevant to human development).

IV. New Data Extend Serotonin Findings to Mammalian Embryos

My published (peer-reviewed) papers show that serotonin functions in LR asymmetry in chick and frog embryos, and that SSRIs can perturb this process and cause laterality defects [12, 16, 22, 37, 38, 78, 81, 100, 101]. I was asked at the Daubert Hearing if there are data that supported my opinions in mammalian or human models (so as to add a check mark to human column on a figure (below as Fig. 9), originally from the Levin 2007 publication, as below).

As figure 1 below shows, mammalian (e.g., rabbit) embryos and chick embryos are extremely similar at early stages – both are a flat disk with primitive streak that demarcates the midline, and thus defines the anatomical left and right sides. In this they differ from highly specialized rodent embryos (which form a cone or cup shape), revealing why chick and rabbit are a better model for understanding human asymmetry (and its defects) than is the mouse or rat.

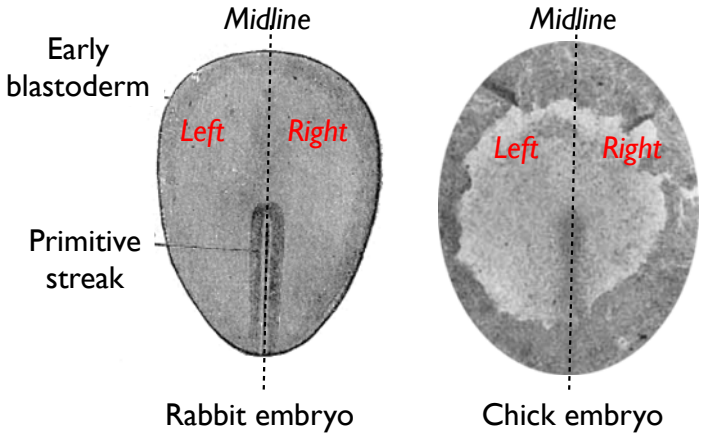


Figure 7: same bodyplan of rabbit and chick embryos

To try to observe the asymmetric localization of serotonin, and the presence of serotonin and SERT in early mammalian embryos, we examined the presence of serotonin and SERT in the early rabbit embryo (Figure 7) using immunohistochemistry. Consistently with my mechanism and what was observed in chick, we detected serotonin to be present on the right side (asymmetrically) of the primitive streak (see blue arrowheads in Fig 2A), as well as the main target of Zoloft - SERT (Fig. 2B, which is localized in circles around the periphery of cells as the serotonin transporter should be). These data demonstrate that the asymmetry of serotonin localization and the presence of the serotonin transporter (blocked by Zoloft) are both conserved to mammalian embryos, thus supporting the stated mechanism and putting an end to the suggestion that there are no relevant data on this mechanism in mammalian systems.

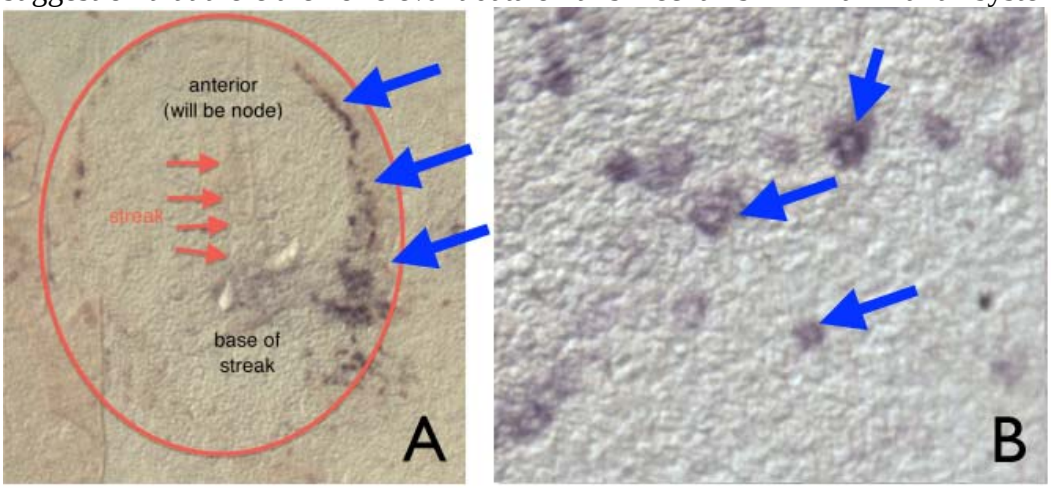


Figure 8: serotonin and its transporter in early rabbit embryos

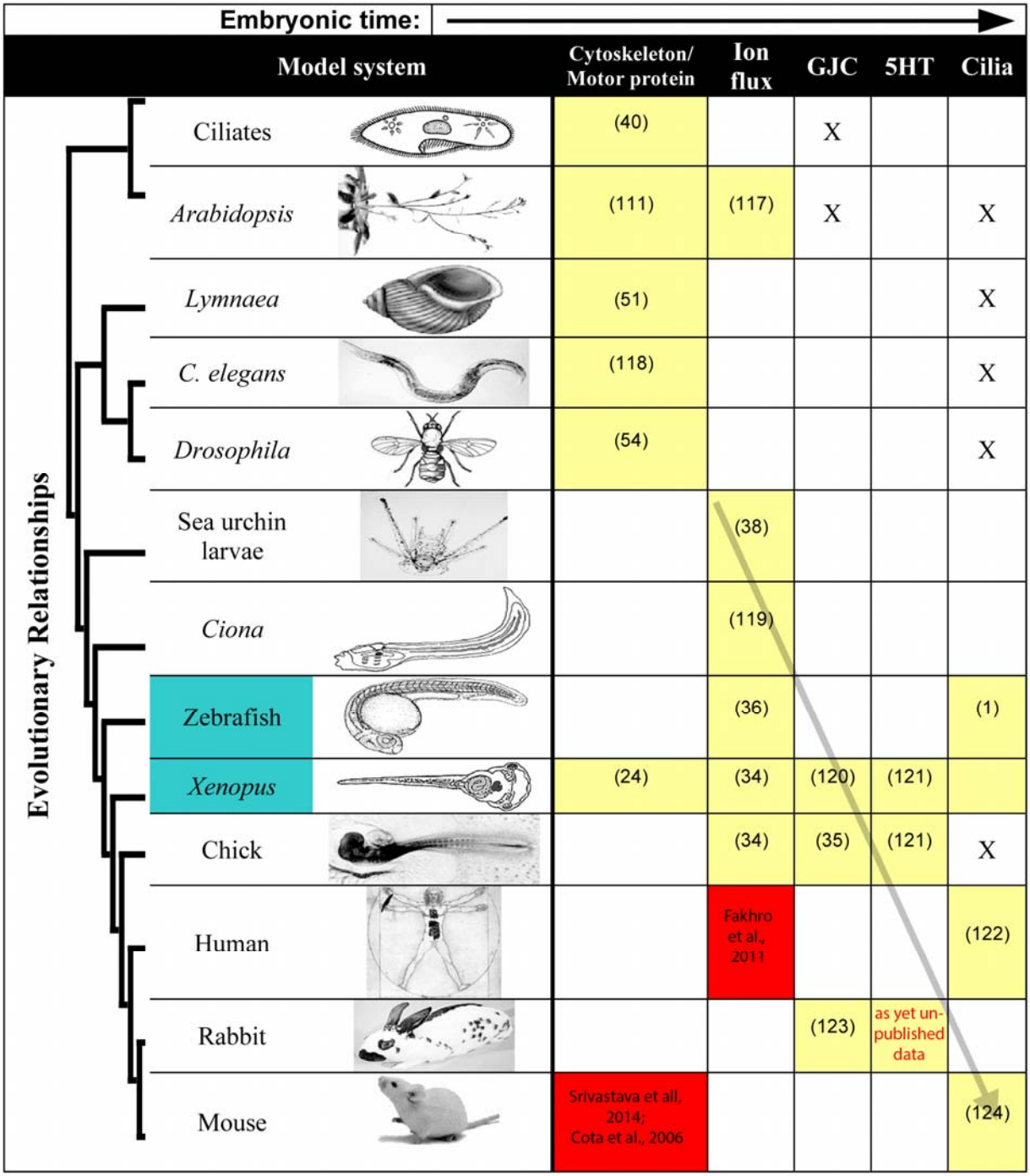
V. Conservation of Ion Channel Mechanism to Human Left-Right Asymmetry

I have long stated in my published papers that the basic early mechanisms of left-right asymmetry are highly conserved throughout the animal kingdom [16, 63, 66, 72, 177]. Our

recent published review compared the various mechanisms and at the time, did not indicate a role for ion transport in humans. **The science has advanced since the Daubert Hearing, and a recent paper [178] indeed showed that 2 ion channels were identified as causing heterotaxy (left-right asymmetry birth defect): SCN1A and SCN9A, which are ion channel genes, revealing that in humans as in other species, ion channel activity is an integral part of left-right patterning.**

Thus, I have updated the table from my recent reviews (Figure 9), to include what is now known: that the ion channel mechanism now extends to humans. Disruption of ion channel genes (whether genetically or by drugs) will perturb the normal process of embryogenesis, as shown in these human patients. Because Zoloft has been shown, in mammalian cells [127, 129, 130], to block a number of ion channels including voltage-gated sodium channels (as are SCN1A and SCN9A), these new data clearly support the relevance of my mechanism for human patients exposed to the teratogen Zoloft.

Figure 9: Conservation of left-right patterning mechanisms among the tree of life



VI. Ion channels are crucial for normal embryogenesis in humans

With respect to the role of ion channels in embryogenesis, new science has emerged. A number of excellent papers have emerged in the recent months [136-140]. These important studies significantly strengthen my opinion that when electrical activity in the developing embryo is affected, by any means, significant birth defects result. Zoloft is known to affect ion

channels – the proteins that control cells' electrical activity. Recent studies have shown that problems with the activity of such channels result in birth defects of the heart, face, brain, and limb, including club foot and other defects.

One study [179] shows that problems with the voltage-gated potassium channel cause Temple-Baraitser syndrome, a developmental disorder affecting the developing face and bony structures of the hands and feet. It should be noted that such potassium channels have long been implicated in embryogenesis by my work in the frog model [76-78], again validating the relevance of our frog work for human medicine. Along the same line, in this paper the authors use frog eggs to study the physical properties of this ion channel, confirming the clinical utility of the data coming from frog cells for understanding human birth defects.

Another study [180] shows that developmental defects (including club foot, Fig. 10) result from a problem with a sodium channel, once again the kind of channel that is targeted by Zoloft [131, 181, 182]:

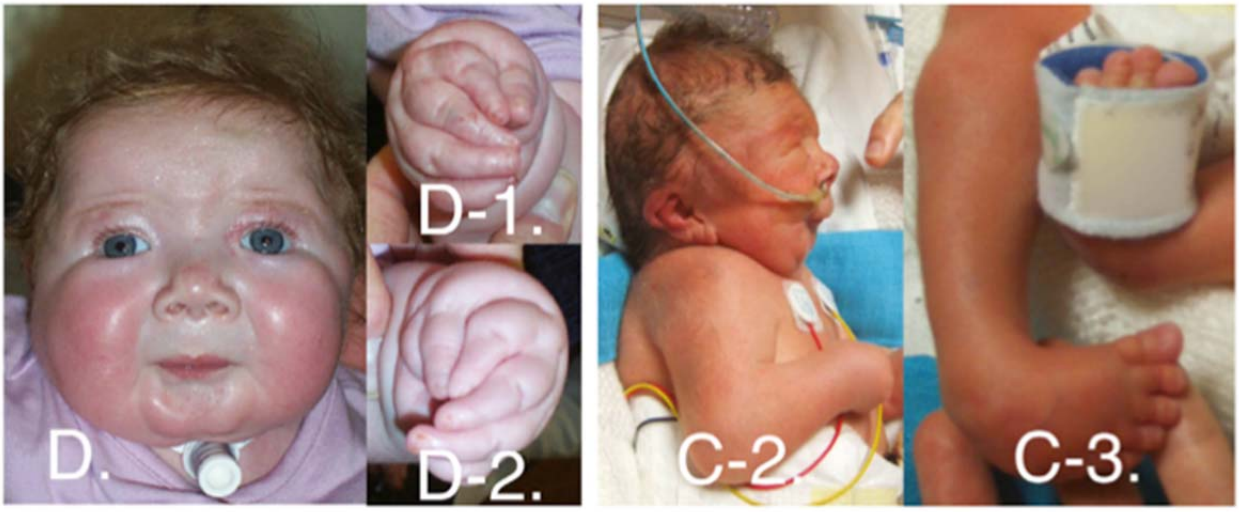
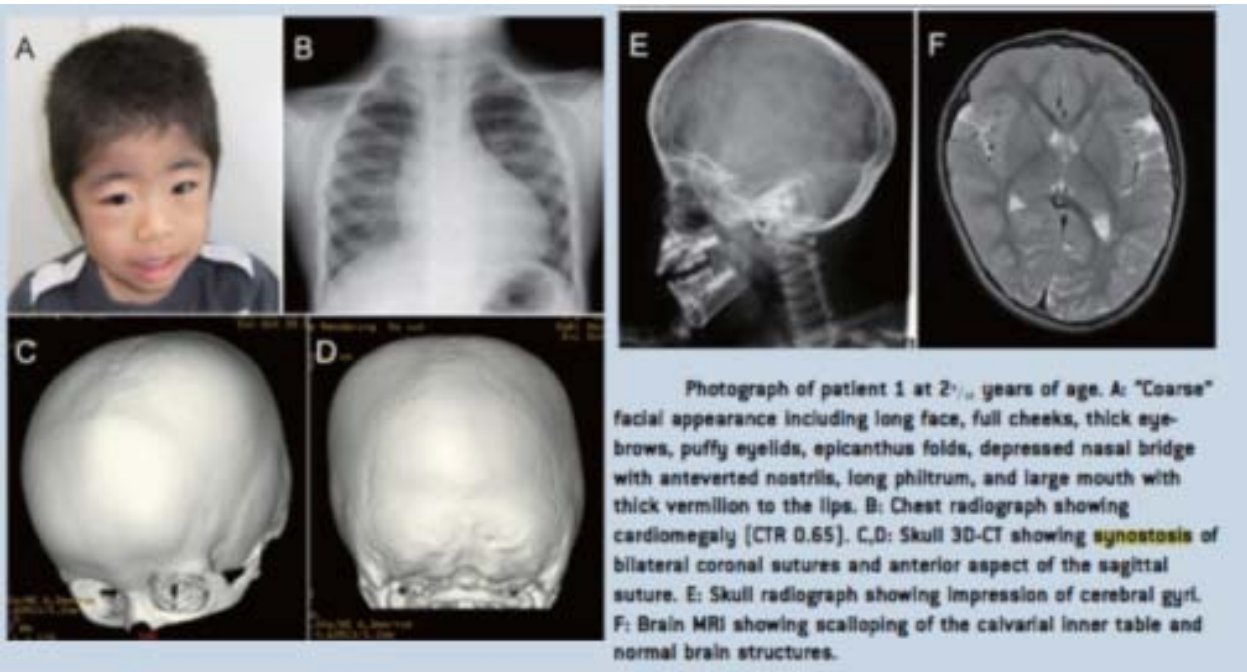


Figure 10 (from [180]) showing developmental malformations induced by ion channel mutations.

In two other papers [183, 184], we learn that Cantu syndrome is caused by a problem with a potassium channel – the same channel my work implicated earlier. This syndrome includes craniosynostosis and aortic malformations.

Figure 11: Cantu – a birth defects syndrome caused by ion channel dysfunction



Photograph of patient 1 at 2½ years of age. A: "Coarse" facial appearance including long face, full cheeks, thick eyebrows, puffy eyelids, epicanthus folds, depressed nasal bridge with anteverted nostrils, long philtrum, and large mouth with thick vermilion to the lips. B: Chest radiograph showing cardiomegaly [CTR 0.65]. C,D: Skull 3D-CT showing synostosis of bilateral coronal sutures and anterior aspect of the sagittal suture. E: Skull radiograph showing impression of cerebral gyri. F: Brain MRI showing scalloping of the calvarial inner table and normal brain structures.

Finally, new data in the MGI Mouse Mutant Database shows that problems with the ion channel HCN4 cause laterality disturbances, linking ion channel dysfunction to asymmetry defects in mammals. My work long ago predicted effects on left-right asymmetry of ion channel disruption in mammals, and these data confirm it in mice (this study was part of the massive "Bench-to-Bassinet" screen, designed to uncover mechanisms of human heart birth defects). Similar studies, such as that of Teng et al. (2008) confirm the link between ion channel dysfunction and cardiovascular birth defects.

(see next page)

b2b1508Clo Chemically induced Allele Detail MGI Mouse (MGI:5437081) 5/18/15 5:05 PM

MGI

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b2b1508Clo

Chemically induced Allele Detail

Nomenclature | Mutation origin | Mutation description | Phenotypes | Find Mice (IMSR) | Notes | References

Nomenclature

Symbol: b2b1508Clo
Name: Mutant line 1508; Bench to Bassinet Program (B2B/CVDC), mutation 1508 Cecilia Lo
MGI ID: MGI:5437081
Synonyms: Oscar
Gene: b2b1508Clo *Location:* unknown

Mutant 1508-006-LA displays heterotaxy, as indicated by levocardia, anterior positioning of the aorta, right pulmonary isomerism, right sided stomach, and abnormal liver lobation

Show the 27 phenotype image(s) involving this allele.

Mutation origin

Strain of Origin: C57BL/6J
Project Collection: B2B/CvDC

MGI_ID	LINE_ID	GENE	VARIANT_TYPE	ANNOTATION	COVERAGE	FREQUENCY	CHR	ZY
5431501	b2b1584Clo	Hcn4	missense	Hcn4:NM_001081192:exon1:c.C584T:p.A195V	34	0.38	9	
5437081	b2b1508Clo	Hcn4	splicing	Hcn4:NM_001081192:exon2:c.1209+2T>G	16	0.44	9	

Mutation description

Allele Type: Chemically induced (ENU)
Mutation: Undefined

This ENU-induced mutation was isolated in a screen at the University of Pittsburgh. (*J:175213*) Additional incidental mutations were detected in sequencing for the causative mutation, b2b1508Clo, and may be present in stocks carrying this mutation.

Phenotypes

Key:

hm	homozygous	ht	heterozygous	tg	involves transgenes
cn	conditional genotype	cx	complex: > 1 genome feature	ot	other: hemizygous, indeterminate,...

√	phenotype observed
N	normal phenotype

Genotypes:

Genotype	Allelic Composition	Genetic Background	Cell Line(s)
hm1	b2b1508Clo/b2b1508Clo	C57BL/6J-b2b1508Clo	

Phenotypes:

Affected Systems (show or hide all annotated terms)	hm1
cardiovascular system	√
endocrine/exocrine glands	√
growth/size/body	√
hematopoietic system	√
immune system	√
liver/biliary system	√
respiratory system	√

View phenotypes for all genotypes (concatenated display).

Find Mice (IMSR)

Mouse strains and cell lines available from the International Mouse Strain Resource (IMSR)

Carrying this Mutation: Mouse Strains: 1 strain available Cell Lines: 0 lines available

Carrying any b2b1508Clo Mutation: 1 strain or line available

Notes

Summative Diagnosis:
Cardiac phenotype: Congenital heart diseases associated with heterotaxy including dextrocardia/mesocardia, transposition of great artery (TGA) with tricuspid atresia, Taussig-Bing type double outlet right ventricle (DORV), atrioventricular septal defect (AVSD), muscular VSD, right sided aortic arch (RAA) and aortic arch anomalies, duplicated inferior vena cava (IVC)
Noncardiac phenotype: Thymus hypoplasia, right pulmonary isomerism, midline liver

Phenotypic Similarity to Human Syndrome: Heterotaxy

Fyler Codes
The Fyler code developed by The Boston Children's Heart Foundation in Boston Children's Hospital provides a hierarchical clinical diagnosis of congenital cardiovascular defects and other disorders. These codes are used to delineate pathology in the mutant mouse models that parallel human disease and can be cross referenced to the International Pediatric and Congenital Cardiac Code (IPCCC) (http://www.ipccc.net/).

Fyler Code ID	Code Description
0190	Heterotaxy Syndrome
0400	Tricuspid atresia
0610	DORV, Taussig bing
0700	D-loop transposition of the great arteries
1100	Atrioventricular canal (endocardial cushion defect)
3804	Congenital heart disease
3950	{S,D,D}
3951	{S,D,L}
3988	{A,L,L}

References

Original: J:175213 Lo C, Information submitted by the NHLBI Cardiovascular Development Consortium (CvDC), Bench to Bassinet Program (B2B/CvDC). MGI Direct Data Submission (B2B/CvDC). 2011-15;

All: 1 reference(s)

Taken together, these new data significantly strengthen body of evidence revealing the ion channel mechanism of action of Zoloft and confirm that together with the serotonergic mechanism, there is a clear link between the mechanism of action of Zoloft and a range of human birth defects, in general and specifically cardiac birth defects, that is demonstrated in reliable scientific data.

VII. New data on Zoloft and pattern formation

One of the model systems used to understand how cells build and assemble organs is Planaria, which are a medically-important (and highly NIH-supported) model species being used to understand stem cell function, immune response, drug addiction, epigenetics, cancer, and body patterning [185-196]. Our latest data in this system (currently being written up for publication, Fig. 12) show that exposure to Zoloft or Prozac can induce formation of a second head, a process that illustrates the fundamental ability of Zoloft and other SSRIs to derange the cellular functions needed to properly assemble a correct bodyplan.

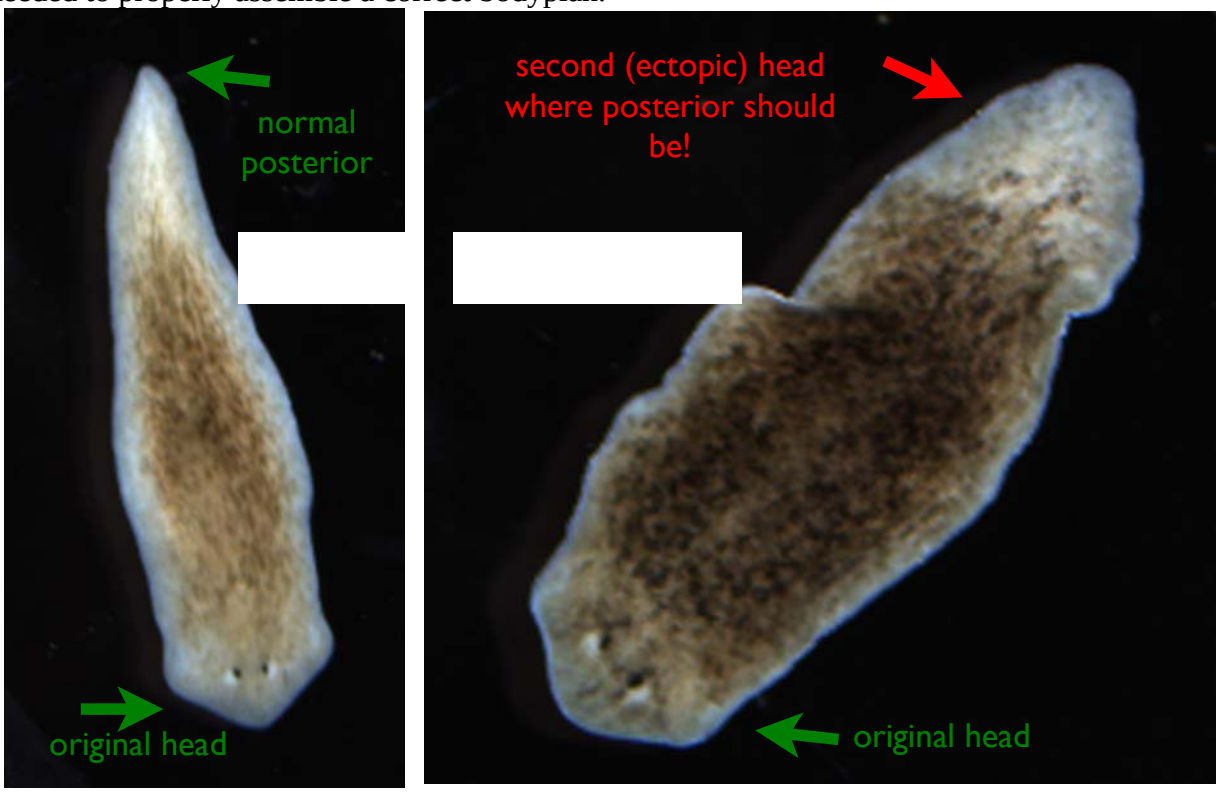

Figure 12: SSRIs disrupt normal body patterning in planaria

Thus, the science clearly shows a causal link between the targets impacted by Zoloft and other SSRIs and birth defects in humans, rodents, and other systems used for biomedical research.

VIII. Conclusion

In conclusion, it is my opinion that published, peer-reviewed, reliable scientific evidence clearly indicates that pathways known to be affected by Zoloft and other SSRIs – serotonin transport and ion channel function – are crucial for normal embryonic development in human and other mammalian and non-mammalian systems. Recent data significantly strengthen my conclusion and provide even better evidence of the same mechanisms in mammals. I recently expressed this opinion in a paper currently in review at *Reproductive Toxicology*. Based on my background, training, experience and review of a scientifically sound body of evidence, it is my professional opinion, as a molecular biologist, that interference with these pathways by SSRI exposure, including Zoloft in utero, is a potential cause or contributing factor to a wide spectrum

of birth defects, including congenital cardiac defects, from a mechanistic standpoint.

IX. Disclosures

I reserve the right to alter or supplement my opinions. Additionally, I reserve the opportunity to testify in my areas of expertise in response to the testimony of Defendant's opinion witnesses. I am being compensated in connection with this matter at my professional rate of $750 per hour.

Dr. Michael Levin
Director, Tufts Center for Regenerative and Developmental Biology
Tufts University
Medford, MA

Appendix 1: CV of Michael Levin, Ph.D

CURRICULUM VITAE

Part I: General Information

DATE PREPARED: 2012 February

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Place of Birth: Moscow, Russia

Education:

Year	*Degree*	*Institution*
1992	B.S. Computer Science and Biology	Tufts University, Medford, MA
1996	Ph.D. Genetics	Harvard Medical School, Boston, MA Clifford J. Tabin, PhD advisor

Postdoctoral Training:

Year	*Title*	*Discipline*	*Place of Training*
1996-2000	Research Fellow	Cell Biology	Harvard Medical School Mark Mercola, post-doc mentor

Forsyth Institute (Harvard Affiliate) Appointments:

Year	*Title*
2000-3003	Assistant Member of the Staff, Dept. of Cytokine Biology
2003-2006	Associate Member of the Staff, Dept. of Cytokine Biology
2006-present	Director & Department Head, Center for Regenerative and Developmental Biology
2007-2009	Senior Member of Staff (equivalent to Full Professor)
2009-present	Senior Research Investigator, Dept. of Molecular Genetics

Academic Appointments:

Year	*Title*	*Institution*
2000-2003	Instructor in Oral and Developmental Biology	Harvard School of Dental Medicine
2003-2004	Assistant Professor of Oral	Harvard School of Dental Medicine

	and Developmental Biology	
2005-2009	Assistant Professor of Developmental Biology	Harvard School of Dental Medicine
2006-present	Adjunct Associate Professor of Biomedical Engineering	Tufts University
2008-2009	Associate Professor of Developmental Biology	Harvard School of Dental Medicine
2008-present	Professor of Biology	Tufts University
2010-present	Visiting Professor of Genetics	Harvard Medical School, Wyss Institute
2011-present	Vannevar Bush Professor	Tufts University

Major Administrative Responsibilities:

Year	*Title*	*Institution*
2002-2006	Chairperson, Seminar Series Personally invited and hosted 61 world-class speakers, including: Mark Mercola, Richard Borgens, Shipeng Yuan, Kyu-Ho Lee, Kelly McLaughlin, Riyi Shi, Angeles Ribera, James Deshler, Philip Newmark, Brenda Brizuela, Peter Vize, Harry Wichtel, Karen Symes, Alex Schier, Ken Robinson, Jeremy Green, Roberto Gaxiola, Harry Witchell, Max Myakishev, Oksana Polesskaya, Frank Conlon, Colin McCaig, Michael Carey and Karl Edminster, Patricia Pietrantonio, Malcolm Whitman, Vladimir Gelfand, Marnie Halpern, Donald Giddon, Charles Abramson, Blanche Schwappache, Iain Drummond, Alejandro Sanchez Alvorado, Ido Kema, Jean Lauder, Laurinda Jaffe, Kaethi Geering, Amy Sater, Nandita Quaderi, Michael Forgac, Hazel Sive, Gerald Schatten, Sally Moody, Mike Danilchik, Rao Sivapradarao, Scott Holly, Greg Beitel, Randy Blakely, Richard Wassersug, Raul Martinez-Zaguilan, Sebastian Shimeld, P. Tsonis, Rebbecca Burdine, Richard Woodruff, Arkhat Abzhanov, Ellen Heber-Katz, Mustafa Djamgoz, Karuna Sampath, Timothy Day, Grace Gill, Guenter Albrecht-Buehler, Stephane Noselli, Bruce Nicolson, Richard Schlegel	Forsyth Institute
2006-2010	**Founder** and Director, Forsyth Center for Regenerative and Developmental Biology	Forsyth Institute
2002-2008	Member, Biological and Biomedical Science Program	Harvard Medical School
2004	Member, Preliminary Qualifying Exam Board (twice)	Harvard Medical School
2006	Organized a satellite symposium at the Society for Developmental Biology Annual Conference	University of Michigan
2008-present	**Founder** and Director Tufts Center for Regenerative and Developmental Biology	Tufts University
2008-present	Professor, Department of Biology	Tufts University
2010-present	Visiting Professor of Genetics, Wyss Institute	Harvard University

Major Committee Assignments:

Year	*Title*	*Institution*
2001-present	Member, Recombinant DNA Committee	Forsyth Institute
2002-present	Standing Committee on Higher Degrees	HSDM
2002-present	Member, Biohazard Committee	Forsyth Institute

2003-present	Member, Hein Fellowship Committee	Forsyth Institute
2004-2006	Member, Zebrafish Facility Transition Committee	Forsyth Institute
2006-present	Forsyth Senior Advisory Committee	Forsyth Institute
2005	Symposium Planning Committee	HSDM/Forsyth
2005-present	Executive Committee Member, Department of Developmental Biology	HSDM
2006-present	Strategic Planning Science & Research Committee	Forsyth Institute
2007-2008	90-Day Committee	Forsyth Institute
2007-present	Senior Governance Committee	Forsyth Institute
2009-2010	Member, BME Faculty Search Committee	Tufts University
2010-2011	Member, Physiologist Faculty Search Committee	Tufts University

Student Mentoring Committee Assignments:

Year	*Title*	*Institution*
2001	Member, Thesis Committee for Ulku Canyurek	HSDM
2004	Member, Qualifying Exam Committee for Sabrina Hom	Harvard Med School
2005	Member, Thesis Evaluation Committee for Geoffrey Grant Whitehead	Harvard Med School
2005	Member, Thesis Evaluation Committee for Nicki Davis	Harvard Med School
2005	Member, Qualifying Exam Committee for Karolina Mizeracka	Harvard Med School
2005-2006	Member, Thesis Committee for Shing-Ming Cheng	Northeastern University
2006	Member, Thesis Evaluation Committee for Amy Jennifer Crystal	Harvard Med School
2006	Member, Thesis Evaluation Committee for Chad Robert Boers	Harvard Med School
2006-2008	Member, Thesis Committee for An Dinh	Tufts University
2006-2011	Member, Thesis Committee for Sarah Sundalacruz	Tufts University
2006-present	Member, Thesis Advisory Committee for Shoshoni Caine	Tufts University
2006	Member, Thesis Review Committee	Tel Aviv University
2007	Member, Qualifying Exam Committee for Nevena Dimova	HSDM
2008	Member, Thesis Evaluation Committee for Laura Anne Lowery	Whitehead Institute (MIT)
2009	Member, Thesis Evaluation Committee for Daniel G. Hechavarria	Tufts University
2009	Member, PQE Committee for Ashley Gibbs	Harvard Med School Biophysics Dept.
2010	Member, Thesis Committee for Marie Tupaj	BME Dept., Tufts University
2012	Member, Thesis Evaluation Committee for Shahan Nercessian	Computer Science Tufts University
2012	Member, Graduate Advisory Committee for Kasey Rodgers, Jessica Mustard	Biology Tufts University

Professional Societies:

Year	*Society*	*Role*
1992-present	Bioelectromagnetics Society	Member
2000-2002	Scientific Council of the American Heart Association	Member
2000-2005	Society for Physical Regulation in Biology and Medicine	Member
2003-2004	American Society for Cell Biology	Member
2003-present	Society for Developmental Biology	Member
2010-2011	Society for Neuroscience	Member

Community Service Related to Professional Work:

Year	*Title/Role*	*Institution*
2002	Presentation regarding risk assessment of environmental electromagnetic fields	Swampscott Town Meeting
2002-2004	Mentor, High School Summer Internship Program (science experience for underpriviledged inner-city high-school kids)	Forsyth Institute
2002-2004	Mentor, RSI program (hands-on Summer research for prodigy kids from around the world)	MIT
2004-present	Ad-Hoc Member, Grant Review Committees	

<u>National:</u>

- Vanderbilt University (Central Discovery Grant)
- National Science Foundation
- National Institute of Health
  - Scientific Review Group 2007/05 ZDA1 MXS-M (26)
  - Scientific Review Group 2009/01 ZDA1 MXS-M (01)
  - Scientific Review Group 2009/01 NTRC
  - F32 NRSAs (2009),
  - EUREKAs for NIGMS (2010)
  - S10 grant for BRLE (2009)
  - NIH 2010/10 ZRG1 MOSS-A (02) M
  - NIH 2012, NIDCR
  - NIH SEDAPA ZDA1 MXH-H
- Science Center programs of the U.S. Department of State
- NSF – ad-hoc reviewer for multiple proposals

<u>International:</u>

- Wellcome Trust, BBSRC Fund (U.K.)
- Austrian Science Fund (Hertha Firnber Award)
- France's National Research Agency ("Blanc" CALLU program)
- Marsden Fund (New Zealand),
- Czech Science Foundation,
- Netherlands Organization for Scientific Research (NWO)
- HFSP (France)
- US-Israel Binational Science Foundation
- European Research Council

2010-present	Advisory Board Committee member for Marine Biological Laboratory's Bell Center for Regenerative Biology and Tissue Engineering

Editorial Boards:

Year	*Role*	*Name*
1997-present	Board Member	Frontier Perspectives
1998-present	Board Member	Journal of Scientific Exploration
2002-present	Board Member	Negative Results in Biomedicine
2007-present	Board Member	Laterality
1998-present	Ad Hoc Reviewer for:	ALIFE 13 Conference, American Journal of Medical Genetics, Behavioural Brain Research, Bioelectromagnetics, BioEssays, Biological Reviews, Biology of Reproduction, BMC Developmental Biology, Brain, Brain Research, Cell and Tissue Research, Circulation Research, Current Biology, Cytoskeleton, Development, Developmental Biology, Developmental Cell, Developmental Dynamics, Epigenomics, Future Medicine, Genes & Development, Differentiation, EMBO Reports, Genesis, Human Reproduction, International Journal of Radiation Biology, Journal of Comparative Physiology A, Journal of Molluscan Studies, Journal of Statistical Physics, Mechanisms of Development, Nature Cell Biology, Nature (*received letter of thanks as a frequent reviewer*), Nature Reviews Genetics, Neuroscience, Pharmacology Biochemistry and Behavior, Physical Biology, PLoS One, PNAS, Proceedings of the Royal Society, Progress in Biophysics and Molecular Biology, Reproductive Toxicology, Science, Stem Cells and Development, Stem Cell Research and Therapy, Symmetry, Teratology, Trends in Cell Biology, Trends in Ecology and Evolution, Trends in Genetics
2008-2009	Guest editor	*Seminars in Cell and Developmental Biology*, two special issues on Regeneration
2011	Guest editor	*Proceedings of the National Academy of Science of the United States*
2012	Guest editor	special issue of *Stem Cells International* on stem cells and ion channels

Awards and Honors:

Year	*Name of Award*
1990, 1991	Hughes Scholarships
1992-1995	NSF pre-doctoral fellowship
1997	Alexander Imich Award, Saybrook Graduate School
1997-2000	Helen Hay Whitney Foundation post-doctoral fellowship
2000	Junior Investigator Award, Society for Physical Regulation in Biology and Medicine

2001	Best Talk Award, Juan March Conference on Left Right Asymmetry, Madrid	
2001	Nominated by Harvard for the Pew Scholarship Award	
2005	My work on asymmetry was selected as "a Milestone in Developmental Biology in the last century" by Nature (#23 at http://www.nature.com/milestones/development/milestones/index.html)	
2007	Established Investigator Award from the American Heart Association	
2009	Invited to give the S. Meryl Rose lecture at Marine Biological Labs, Woods Hole	
2011	Vannevar Bush endowed Chair appointment	Tufts University
2012	Scientist of Vision Award,	IFESS society
2013	Distinguished Scholar Award,	Tufts University

Part II: Research and Teaching Contributions

A. Research Focus

Overview

My group focuses on the dynamics of information processing in living tissues. Specifically we study spatial information (which underlies the ability of organisms to create, maintain, and repair complex geometrical shapes) and temporal information (dynamics of memory and learning within a changing brain and CNS). Using molecular genetics, biophysics, developmental biology, and computational modeling we work in the fields of embryonic development, regeneration, and cancer. Fundamentally we view all of these problems as examples of a complex dynamical system that establishes and maintains shape; we seek to understand and learn to control the processes by which individual cell behaviors are orchestrated towards large-scale anatomical needs of the host organism. Applications extend to the control of growth and form to address birth defects, regenerative medicine, and synthetic bioengineering.

Specifically, we focus on endogenous bioelectric signals – gradients of transmembrane potential in non-neural cells that provide instructive cues during pattern formation. We developed the first genetic tools allowing these bioelectric prepatterns to be visualized *in vivo* and, most crucially, to be modulated with molecular precision in loss- and gain-of-function studies. Using model systems such as zebrafish, Xenopus, chick, and planaria, as well as mouse and human cells with collaborators, we showed that voltage gradients not only modulate basic cell behaviors but also determine positional information and organ identity. For the first time, we have dissected the pathways that lead from the production of gradients by ion channel proteins, through the transduction machinery that turns a fundamentally biophysical event into second-messenger cascades, to known epigenetic and genetic downstream cascades. This work reveals fascinating and novel aspects of basic biology and is expected to produce new modalities for manipulating tissue growth for biomedical applications. It is complemented by computational analyses of the auto-catalysis of patterns in physiological networks (the non-genetic origin of patterning in tissues).

Our projects often blur the distinction between computation in the nervous system and pattern formation. At the boundary of the brain:body interface, projects include the dynamics of memories during brain regeneration in planaria, the plasticity of the tadpole brain as it uses ectopic eyes on its tail for vision, and the guidance of shape during tadpole tail regeneration by the brain and CNS. Another section of the group works on developing a new bioinformatics of shape – artificial intelligence tools to mine functional data in developmental genetics to help formulate

mechanistic, constructive models of pattern formation (going beyond sequence and gene networks to assist scientists in deriving testable algorithmic models of actual anatomy).

Key recent advances

(1) We discovered that endogenous ion fluxes play a conserved and crucial role in the constsnet left-right (LR) patterning of the heart, viscera, and brain in embryos. We developed a new screening methodology that uncovered 4 transporters that are asymmetrically localized at extremely early stages and produce K^+ and H^+ flows upstream of asymmetric gene expression. This work identified a novel mechanism in asymmetry, showed that embryos align the LR axis long prior to previous thought in the field (a significant break with the currently-popular paradigm for late, cilia-dependent mechanisms), and uncovered new localization zipcodes for proteins in embryonic cells. We are molecularly characterizing the function of each of the transporters and integrating this information into a predictive, quantitative model of developmental physiology that amplifies single-cell chirality information into true asymmetry of multicellular fields.

(2) We discovered that the neurotransmitter Serotonin controls developmental patterning in chick/frog embryos long before neurogenesis, identifying a novel role and alternative signaling mechanism for a biomedically-important neurotransmitter, and revealing an aspect of patterning dependent on the dynamic movement of non-protein small molecules. It turns out that in frog embryos, serotonin is a morphogen moved through a cell field by an electrophoretic force in embryos as a positional signal along the left-right axis. We are characterizing the functions of pre-nervous serotonin, and have identified a novel intracellular receptor which, through its interactions with HDAC1, explains how early serotonin movement epigenetically regulates the transcription of the first asymmetric gene (Nodal).

(3) In regeneration, we uncovered novel roles for ion flows in anterior-posterior patterning in planaria and in tail regeneration in tadpoles. We identified and characterized electrogenic pumps producing striking voltage gradients during regeneration and showed that these are necessary and sufficient for regeneration of the spinal cord and muscle in tadpole tails. We also showed that the flow of ions and small molecule signals through gap junctions are part of the mechanism by which fragments of flatworms determine which end should form the head and which should form the tail. We showed that we can modulate these signals to exert control over the large-scale structure of the regenerate – using bioelectrical signals (delivered genetically or pharmacologically, not through electric field application) to determine the shape of structures built by the animal's adult stem cells. In the Xenopus system, having characterized the role of ion gradients in tail regeneration, we developed a small molecule drug cocktail that takes advantage of endogenous channels to induce the regeneration of complete legs in froglets! We are currently moving this technology to a rat limb amputation models with collaborators in the Biomedical Engineering department.

(4) We discovered a specific manipulation of transmembrane potential that can turn any region of the frog embryo (even gut endoderm and lateral plate mesoderm) into complete, functional eyes, suggesting important revisions to the current picture of competence restrictions in cell lineages. We also traced the genetic pathway leading from the voltage change to eye morphogenesis (including transduction and transcriptional responses), and are now moving this into a murine model for applications to eye repair. On the basic biology side, we are using this as our first entrypoint to breaking the bioelectric code. We found other membrane voltage changes that result in the development of hearts, otoliths, limbs, and other structures. To fully dissect the mapping between tissue voltage properties and resultant anatomy, we recently published the first use of ion channel optogenetics in non-neural cells, inducing regeneration by light signaling to halorhodopsin-bearing blastema cells. We are now extending this approach to use optogenetics to allow us to read and write bioelectric information directly into actively patterning tissues *in vivo*.

(5) Our work on the bioelectric basis of the morphogenetic disorder of cancer identified a) a non-genetic (bioelectric) switch in their microenvironment that confers a tumor-like phenotype

on some somatic cells, b) a physiological signature by which pre-cancerous cells can be recognized non-invasively, and c) a hyperpolarizing regime that suppresses oncogene-mediated tumorigenesis. The work in the frog model is being used to understand bioelectric properties as a signature and functional trigger point by which cells can be normalized or driven to cancer, and with collaborators in the field of melanoma is being moved towards applications for a biomedical detection and treatment technology.

(5) We designed and built a state-of-the-art parallelized (high throughput) computer-controlled device to probe mechanisms of memory and learning in genetically-modified flatworms and *Xenopus* tadpoles. This device is the first system able to provide individual real-time feedback to each animal (allowing not just tracking but sophisticated classical conditioning and instrumental learning paradigms); we used it to show that animals bearing eyes only on their tails could learn perfectly well in visual recognition tasks, and that animals with reversals of left-right asymmetry showed interesting cognitive phenotypes on non-lateralized tasks (generalized learning and memory assays). The system is well-suited for pharmaceutical drug screens designed to identify novel neuroactive compounds such as memory-enhancing nootropics.

Future directions

On the fundamental theory side, my plan for the next 5 years is to develop predictive, quantitative models of complex pattern formation using techniques from cognitive science and artificial intelligence. We will model developing systems as cognitive agents that perform decision-making to achieve target morphology to develop much better predictive control over growth and form in a number of tractable model systems. This will involve not only modeling and application of concepts such as top-down algorithmic control and swarm intelligence to cell behavior, but also development of high-resolution models of information storage and manipulation in physiological networks (treating non-neural cells as neural net-like computational tissues).

At the bench, we will integrate the above theory with continued work on the bioelectric basis of pattern formation. Moving forward to a better understanding of the bioelectric code, we will transition some of our technologies in cancer and regeneration to mammalian systems with an eye towards biomedical applications. An important future line of investigation is to extend synthetic biology – providing a set of bioelectric building blocks and modeling results to augment the existing transcriptional toolkits, we will attempt to move beyond soups of individual cells to achieve guided self-assembly and repair of complex shapes by multicellular tissues.

My group functions as a hub of many collaborators in computer science, biomedical engineering, and biology to mine one central cohesive theme: the computational, constructive understanding of information processed by tissues and organs and its exploitation for the many areas of biology and medicine in which control of biological growth and form is paramount.

B. Teaching and Mentoring

I have taught numerous classes at institutions such as Harvard, Tufts, Boston University, NorthEastern University, MIT, etc. and am frequently invited to give specialty seminars to graduates and undergraduates on asymmetry, mathematical modeling, biophysics of morphogenesis, etc. In the past few years, I have taught for Harvard Medical School courses including 1) BBS Genetics 330 (2006, a complete semester, co-taught with Andrius Kazlauskas), 2) the HSDM Craniofacial Development course (2007 & 2008, organized by Leslie Will, where I lectured and led discussion sections on mechanisms of laterality as they relate to craniofacial patterning), 3) BBS DB207 (Developmental Biology course led by Andrew Lassar), where I presented molecular aspects of embryonic left-right patterning in 2004, 2005, and 2006, 4) The HST program's 521 course on Biomaterials and Tissue Engineering where I have taught in numerous years, and 5) the Woods Hole Embryology Course where I taught on left-right asymmetry mechanisms throughout phyla in 2007 and 2009. My favorite aspect of teaching is

presenting inter-disciplinary approaches to non-specialists: I've given classes on complex systems analysis to forestry students at Essex Agricultural College, and have also taught seminars on computer science for biologists, and biology for engineers. In addition to formal lecturing, my teaching roles have included personal mentoring of numerous HSDM/HMS rotation and graduate students in my laboratory, as well as undergraduates and high-school students doing internships in my group over the last 5 years. I have greatly enjoyed mentoring at all levels, from high-school to post-doctoral; several of the undergraduate and pre-college students who performed projects in my lab have gone on to win prestigious awards for their work here. At Tufts I participate in teaching a hands-on Experiments in Cell Biology course (Bio52, for undergraduates) and a course in dissecting the primary scientific literature (Bio243, for graduate students), as well as a course for Bioengineers (BME164).

C. Research Funding Information

Funding status:

A total of twenty two competitive, extramural grants have been awarded to the PI since the lab opened. These include both federal and non-federal sources.

Years	*Funding Source*	*Role*	*Grant Title*
2001-2003	American Heart Association (Beginning Grant-In-Aid)	PI	Pre-nervous Functions of Serotonin
2001-2004	The Medical Foundation (New Investigator Award)	PI	The Role of K_{atp} Ion Channels in Embryonic Development
2002-2005	American Cancer Society (Research Scholar Grant)	PI	The Role of Ion Channels and Pumps in Embryonic Development
2003-2006	National Science Foundation (Standard Grant)	PI	The Role of Serotonin in Left-Right Patterning
2003-2008	National Institutes of Health (R01)	PI	The Role of Ductin in Embryonic Development
2004-2006	National Institutes of Health (R21)	PI	Cellular Learning and Information Outside of the Brain
2004-2006	National Science Foundation (Instrument Development Grant)	PI	A Device for Automated Large-Scale Morphological and Behavioral Screening
2004-2007	March of Dimes (Standard Grant)	PI	The Role of K^+ Channels in Embryonic Laterality
2004-2009	National Science Foundation (Career Award)	PI	The Biophysics of Flatworm Regeneration
2006-2010	U.S. Dept. of Transportation (Federal Appropriation)	PI	Study of Regenerative and Developmental Biology for Replacing Tissue Lost or Damaged as a Result of Accidental Injuries
2007-2011	American Heart Association (Established Investigator Award)	PI	Molecular Analysis of Serotonin Signaling in Establishing Heart Laterality
2007-2009	National Institutes of Health (R21)	PI	Specific ion flows: a novel signal Mediating Stem Cell-Niche Communication
2007-2011	National Institutes of Health (R01)	PI	Bioelectrical Controls of Left-Right Asymmetry

2008-2011	National Institutes of Health (R01)	PI	Bioelectric Mechanisms of Eye Induction
2008-2011	Mathers Foundation (R01-scale)	PI	Quantitative Analysis of Memory in Flatworms
2008-2012	National Institutes of Health (R01)	PI	Bioelectrical Controls of Tail Regeneration
2010-2011	National Institutes of Health (R01)	PI	Automated Analysis of Learning in Vertebrates
2010-2012	DOD (Subcontract with Forsyth Institute)	PI	Limb Regeneration through Bioelectricity
2010-2012	NIH (R01)	Co-PI	Tissue Regeneration by Biophysical Signaling
2010-2012	NIH C06, co-PI (Robert Sternberg was PI),		Collaborative cluster in Genome Structure and Developmental Patterning
2011-2014	Mathers Foundation	PI	Probing the Fundamental Nature of Bioelectric Signals that Mediate Information Processing in Cells and Tissues
2011-2014	NSF	PI	A computer framework for modeling complex pattern formation
2012-2013	NSF (subcontract with MIT)	PI	Control of in vivo developmental pattern formation via a new large-scale optogenetic workstation: opportunities for bioengineering, synthetic biology, and regenerative medicine
2012-2013	DARPA (subcontract with North Shore Health System)	PI	An organ regeneration model in the Xenopus laevis system
2012-2015	NSF	PI	A workstation for optogenetics for embryogenesis and regeneration
2013	Silicon Mechanics	PI	Cluster Supercomputer awarded

D. Current and Past Research Activities other than those mentioned above

1. Four inventions and two provisional patent applications filed so far on biomedical applications of novel pathways uncovered in the lab.
2. Organized a satellite symposium at the 2006 Society for Developmental Biology Annual Conference. This symposium explored interdisciplinary aspects of biological polarity, and featured 8 nationally known speakers. The symposium was very well attended and received excellent feedback.
3. Wrote a monograph on the husbandry of *Xenopus* and the running of a frog facility, which is being distributed to the community and will allow easrly-stage PIs to begin using this versatile experimental system. This is a service to the field because it provides detailed instructions, construction details, and protocols that will save labs much time and money in setting up a usable *Xenopus* colony.
4. Collaborations within Forsyth:
   a) Yi-Ping Li – "Role and mechanism of CNBP in directing mouse forebrain development"
   b) Enrst Reichenberger – consultant on ANK project
   c) Paloma Valverde – "Role of KBF1 and KBF1-related factors in the transcriptional regulation of the voltage-gated potassium channel Kv1.5" R03 application

d) Pam Yelick – "Gap-junctional communication in zebrafish" R21 application
e) Zie Skobe – participant on the institutional grant to acquire confocal scope (funded)
f) Doug Hanson – participant on institutional grant for image management system (funded)
g) Yi-Ping Li – participant on institutional grant to acquire transgenic mouse facility

5. Existing collaborations with Tufts Faculty

In addition to serving on numerous committees for Tufts graduate students, my lab has an active on-going collaboration with David Kaplan in BME at Tufts Engineering, on the biophysical controls of adult stem cell function in egenerative medicine, and with Barry Trimmer, on developing genetic algorithm tools for the formulation of mechanistic models of development and soft-body robot movement. Strong areas of synergy and proposed future collaborations exist with the Tufts Cognitive Science Center, as well as faculty in the Biology, Psychology, and Computer Science departments.

6. National and International Collaborations (Currently Active - not including past)
a) Donal Ingber - Children's Hospital, Harvard, Wyss
b) Federico Calegari – Max Planck Institute, Germany
c) Pamela Yelick – Tufts Medical School
d) Mustafa Djamgoz – Imperial College, U.K.
e) Hans Oberleithner – University of Muenster, Germany
f) Yasushi Okamura – NIPS, Japan
g) Takashi Gojobori - NIG, Japan
h) Seb Shimeld - University of Reading, U.K.
i) David Mooney- Harvard University
j) Guiscard Seebohm - Universität Tuebingen, Germany
k) Andrew Adamatzky – University of the West of England
l) Stephane Noselli - Univ. Nice Sophia-Antipolis, France
m) Colin Nichols – Giovanni Pezzulo, IST-CNR, Italy
n) Joshua Bongard – University of Vermont
o) Christine Pullar - University of Leicester
p) Mary Hendrix – University of Illinois, Chicago
q) Jingsong Xu – University of Illinois, Chicago

7. Advised high school students on research projects: Ashley Bae (Milton Academy), Vokas Arun (Lakeside High School, Seattle WA), Shannon Sample (teacher at Seneca High School, Missouri), Suzanne Michaud (teacher at Holmdel High School, NJ), Andrea Low (Coalfield High School), Jenny Goff (Cheltenham High School, PA), Alicia Urrutia (Eyer Middle School), Ruth Urrutia (Emmaus High School, PA)

8. Wrote letters for Tenure and Promotion cases:
- Amy Sater (University of Houston)
- Nannette Nascone-Yoder (North Carolina State University)
- Tracie Ferreira (UMass Dartmouth)
- Mark Messerli (MBL)
- Michael Zuber (SUNY Medical University)

9. Member of NSF-funded IGERT program at Tufts

10. Publicity and media outreach:
- TV interview on WGBH "Science for the Public"
http://www.scienceforthepublic.org/speakers-guests/meet-michael-levin-phd-/
- Cover story of *Physics Today* for March 2013
- https://www.readmatter.com/a/electric-shock/

11. Organized a symposium – conference on Biologically Inspired Information Processing (http://sites.tufts.edu/biip2012); acquired funding support from Exomedicine Institute.

E. Report of Teaching

1. Local Contributions

a. Courses taught

2000	Developmental Biology, Harvard Medical School. 1 lecture and 1 discussion session. Most of the 10 students were graduate students. The lecture required 6 hours of preparation time and 4 hours of contact time with the students.
2000	Developmental Biology, Tufts Medical School. This lecture was for 15 graduate students. It required 4 hours or preparation time and 3 hours of student contact.
2000, 2002	Developmental Biology, Boston University Medical School. This lecture was for 15 graduate students. It required 4 hours or preparation time and 3 hours of student contact.
2002	Forsyth Institute. This lecture on developmental biology was for 6 undergraduate Dental Hygiene students. It required 5 hours or preparation time and 2 hours of student contact.
2003-2005	Developmental Biology, Whitehead Institute, MIT. These lectures were for 10-15 graduate students. Each required 4 hours or preparation time and 3 hours of student contact.
2006	Co-taught Genetics 330 (HMS) – proposal-writing course, which required 24 hours of student contact time and 12 hours of prep time.
200-2008	Teach asymmetry lectures for graduate students at HMS CB207 (2 hours of student contact time and 2 hours of prep time each year).
2007	Taught asymmetry lectures at Molecular Embryology course at Marine Biological Laboratory, Woods Hole (6 hours of prep time, 4 hours of student contact).
2007, 2008	HSDM lecture on left-right patterning (2 hours of student contact, 4 hours of prep time).
2008	HMS/MIT Health Science and Technology program lecture on regenerative medicine and developmental biology (2 hours of student contact, 4 hours of prep time).
2008-2009	Participated in Bio16, BME 164, Bio 174, Bio 243, COMP 150 ECP (Evolution of Cognitive Processes) at Tufts University (10 hours of prep time, 30 hours of student contact).
2008-2010	Co-taught Bio52 and Bio243 at Tufts University
2009	Guest lecture at HST-521 (Fred Schoen's course) at HMS/MIT (2 hours of student contact, 4 hours of prep time).
2010	Organizer for Bio52. Taught also at BME164.
2011,2012	Participated in Bio52, Bio174, Bio243
2011,2012	Guest instructor, HST 521 Biomaterials, Tissue Engineering and Regenerative Therapeutics at the Harvard-MIT Division of Health Sciences and Technology

b. Invited presentations (not including scientific seminars)

2001	Science Writers Group, Forsyth Institute. "Developmental biology and biophysics"

2001	Danesh Moazed's seminar on how post-docs should look for research jobs, Harvard Medical School. "Finding jobs in academic biology"
2001, 2003	Poster Presentation, Harvard Medical School Trustees "Developmental biology research in the Levin Lab"
2002	Animal Use Committee, Forsyth Institute "Use of the Xenopus model system in developmental biology and related fields"
2003	Scientific Advisory Committee, Harvard School of Dental Medicine "Developmental biophysics research in the Levin Lab"

c. Names of advisees or trainees

Duration of Training	*Name*	*Position While Trainee*	*Current Position*
2001-2002	Daniel Nazarenko	Post-Doc	Toxicologist at Alkermes, Inc., Cambridge, MA
2001-2005	Taisaku Nogi	Post-Doc	Post-Doc at the University of Minnesota
2002	Caitlin Mueller	Undergraduate Student Intern	M.I.T. Undergraduate Student
2002-2004	Emily Yuan	High School Student Intern (Her project in my lab was the winner of MA State Science Fair)	Harvard Undergraduate Student
2002-2004	Ivy Chen	HSDM Graduate Student (graduated with Honors)	Private DDS Practice
2002-2005	Takahiro Fukumoto	Post-Doc	Heads his own group at Wakayma Medical University
2002-present	Dany Adams	Post-Doc	Associate Research Professor, Tufts University
2003	Tim Hsiau	High School Intern (His project in my lab was a semifinalist at the Intel Talent Search)	Washington University Undergraduate Student
2003-2005	Alessio Masi	Post-Doc	Currently has a research position at the University of Florence

2004	Olga Mandelshtam	MIT RSI Program Student Intern	(Unknown)
2004-2006	Caitlin Hicks	Undergraduate Student Intern (*Suma cum Laude* thesis from Harvard for her honors project performed in my lab)	M.D. student at Cleveland Clinic, OH
2004-present	Sherry Aw	Graduate Student, Biological and Biomedical Science Program, HMS	Post-doc, Duke-NUS Graduate Medical School
2004-present	Junji Morokuma	Research Associate	(Continuing)
2005-2010	Nestor Oviedo	Post-doc	PI at UC-Merced
2006-2012	Kelly Tseng	Post-doc	PI at ULVN
2007-present	Douglas Blackiston	Post-doc, NIH T32	(Continuing)
2008-2013	Laura Vandenberg	Post-doc, NIH F32	PI at UMass Amherst
2008-2009	Wendy Zhang	Post-doc	Research Scientist at NIH
2008-present	Wendy Beane	Post-doc, NIH F32	(Continuing)
2008-2010	Katia Carneiro	Post-doc, Pew fellow	PI at Federal University of Rio de Janeiro, Brazil
2009-present	Vaibhav Pai	Post-doc	(Continuing)
2009-present	Brook Chernet	Ph.D. student	(Continuing)
2009-2012	Tal Shomrat	Post-doc	
2009-2010	Claire Stevenson	Undergraduate	PhD student, U. Illinois
2009-2010	Brian Pennarola	Undergraduate	
2009-present	Maria Lobikin	Ph.D. student	(Continuing)
2010-present	Chris Bredie	Undergraduate	
2010-present	Linda Le	Undergraduate	
2010-present	Brian Pennarola	Undergraduate	
2010-present	Mary Rose Branch	Undergraduate	Emory University
2011-present	Rebecca DiBiase	Undergraduate	
2011-present	Emma Marshall	Undergraduate	
2011-present	Max Kachalov	Undergraduate	
2011-present	Arya Saniee	Undergraduate	
2011-present	Garrett Friedman	Undergraduate	
2011-present	Lorraine Eastham	Undergraduate	
2011-present	Brian Tummon	Undergraduate advisee	(Continuing)
2011-present	Jae Sung Hwang	Undergraduate advisee	(Continuing)
2011-present	Jordan Skeens	Undergraduate advisee	(Continuing)
2011-present	Amy Thurber	Grad Student (on committee)	(Continuing)
2011-present	Shoshoni Caine	Grad Student (on committee)	(Continuing)
2011-present	Sarah Sundelacruz	Grad Student (on committee)	
2011-present	Marie Tupaj	Grad Student (on committee)	
2011-2012	Nidhi Chillara	Undergraduate	
2011-2012	Clara Bieck	Undergraduate	

2011-2012	Victoria Tang	Undergraduate	
2011-present	Xiaoteng (Allen) Su	Grad Student advisee	(Continuing)
2011-present	Jessica Mustard	Grad Student	(Continuing)
2011-present	Daniel Lobo	Post-doc	(Continuing)
2012	Kyle Jewhurst	Grad Student rotation	
2012-present	Jean-Francois Pare	Post-doc	(Continuing)
2012-present	Taylor Malone	Undergraduate	(Continuing)
2012-present	Kelly G. Sullivan	Undergraduate	(Continuing)
2012-present	Fallon Schuler	PhD student	(Continuint)
2012-present	Jessica Mustard	PhD student	(Continuing)
2012-present	Hayley Weiss	Undergraduate	(Continuing)
2012-present	Allison Stradiotto	Undergraduate	(Continuing)
2012-present	Elizabeth Tkachenko	Undergraduate	(Continuing)
2012-present	Undergraduate advisees: Emma Marshall, James Holt, Justin Chang, Jordan Skeens, Je Meen Kim, Maxwell Leonhardt, Nicholas Lordi, Katherine McDonnell, Ivanna Mejia, Annaick Miller, Emily Miller, Kristine Ng Sang, Thomas Ollerhead, Sarah Perlo		

2. Invited Lectures

Local/Regional

1996	Essex Agricultural College – Workshop: “Mathematical modeling of biological systems” for undergraduate and graduate students (about 4 hours of preparation time and 2.5 hours of contact time with students).
1998	Banbury Conference on Left-Right Asymetry (Cold Spring Harbor) "Role of gap junctional communication in early left-right patterning"
2000, 2001	Tufts Medical School Seminar Series "Role of gap junctional communication and ion channels in early left-right patterning"
2001, 2004	N.E. Regional Developmental Biology meetings at Woods Hole "Biophysical signals in early left-right patterning"
2003	B.U. School of Medicine, Dept. of Biochemistry "Molecular mechanisms of left-right patterning"
2003	B.U. Dept. of Biology "Biophysical signals in early left-right patterning"
2003	B.U. Dept. of Pathology "Biophysical signals in early left-right patterning"
2003	Rhode Island College "Electric embryos: endogenous ion fluxes control morphogenesis"
2003, 2004, 2005	MIT’s Whitehead Institute "Molecular mechanisms of left-right patterning"
2004	Mass. General Hospital "Electric embryos: ion transport in embryonic patterning"
2004	Harvard Medical School, Development and Neoplasia Symposium in Honor of Dr. Sklar
2005	Tufts Medical School "Bioelectrical signals in embryonic patterning"
2006	Weill Medical College, Cornell (NY) "Bioelectrical signals in embryonic patterning and regeneration"
2006	B. U. Medical Center

2006	"Biophysical controls of embryonic patterning" Middlebury College (VT) "Bioelectrical signals in embryonic patterning and regeneration"
2007	Harvard Medical School, Tissue Healing/Regeneration Symposium "Bioelectrical controls of regeneration and morphogenesis"
2007	Harvard Medical School, IDB Seminar Series "Bioelectrical controls of embryogenesis and regeneration"
2009	Boston University, "Bioelectric mechanisms of morphogenesis"
2009	Spoke at Tufts Medical School Vision Retreat
2009	Keynote Speaker at Tufts University Medical School retreat
2011	Invited seminar speaker, Center of Cancer System Biology, St. Elizabeth's Medical Center, "Bioelectric determinants of cancer"
2011	Invited seminar speaker, University of Connecticut, Department of Physiology and Neurobiology "Endogenous bioelectric signals as determinants of growth and form"
2011	Invited seminar speaker, Mount Desert Island Laboratories (Jackson Labs), Maine "Molecular bioelectricity in development, regeneration, and cancer"
2011	Invited seminar speaker, IEEE EMBS meeting, Boston "Endogenous bioelectricity in development, regeneration, and cancer: molecular mechanisms and biomedical opportunities"
2011	Invited seminar speaker, University of Massachusetts, Lowell "Endogenous bioelectricity in development, regeneration, and cancer: molecular mechanisms and biomedical opportunities"
2012	Invited seminar speaker, Maine Medical Research Institute "Endogenous bioelectricity in development, regeneration, and
2012	Invited seminar speaker, Boston University "Endogenous bioelectricity in development, regeneration, and cancer: molecular mechanisms and biomedical opportunities"
2012	Tufts University Medical Center "Bioelectrical aspects of the microenvironment in cancer"

National

1999	Chirality Congress, Orlando, Florida "Role of gap junctional communication and ion pumps in early left right patterning"
1999	Physical Regulation Society, Florida (Won "Young Investigator" prize): "Role of gap junctional communication and ion pumps in early left-right patterning"
2003	Purdue University "Electric embryos: ion transport in embryonic patterning"
2004	Johns Hopkins/Carnegie Institute "Electric embryos: ion transport in embryonic patterning"
2006	"Bioelectrical signaling in vertebrate regeneration" Society for Developmental Biology, National Meeting, Satellite symposium on biophysical signals in development
2007	**Keystone Symposium** on Tissue Engineering and Developmental Biology, Utah

	"Bioelectrical controls of vertebrate regeneration"
2007	Experimental Biology 2007 Symposium, Washington D.C. "Bioelectrical controls of cell behavior"
2007	Minnesota Stem Cell Institute "Bioelectrical controls of regeneration"
2007	Mayo Clinic "Bioelectrical controls of regeneration"
2008	National Institute of Health, invited speaker at workshop Transforming Regenerative Medicine "Epigenetic, biophysical approaches to cellular control"
1998, 2000 2004, 2008	**Gordon Conferences** on Developmental Biology, Developmental Physiology, Bioelectrochemistry; invited speaker: "Gap Junctional signals in left-right patterning", "Role of ion transporters in left-right patterning", "Role of ion transporters in regeneration of vertebrate muscle and spinal cord", "Perspectives in Bioelectric signaling in development and regeneration"
2009	Vanderbilt University, "Biophysics of embryogenesis"
2009	University of Utah, Neuroscience Department, "Biophysics of morphogenesis"
2010	Gordon Research Conference on Bioelectrochemistry, invited speaker, "Transmembrane potential gradients as regulators of regeneration, development, and neoplasm"
2010	Invited seminar speaker, Ion Channel unit at Duke University, NC "Ion channels and pumps as determinants of pattern formation"
2009,2010,2011	Invited speaker at TMEN Meeting at NIH NCI "Bioelectric determinants of cancer"
2010	Invited seminar speaker, Physics Department, Yale University "Bioelectric controls of cell behavior"
2010	Invited seminar speaker, NIH NCI Frederick, MD "Early mechanisms of left-right patterning
2011	Keynote Speaker, Gordon Research Symposium (Gordon Conference)
2011	Invited seminar speaker, Cincinnati Children's Hospital Research Foundation "Endogenous bioelectricity in development, regeneration, and cancer: molecular mechanisms and biomedical opportunities"
2012	Invited seminar speaker, University of Illinois, Urbana "Endogenous bioelectricity in development, regeneration, and cancer: molecular mechanisms and biomedical opportunities"
2012	Invited seminar speaker, NIH OPSO symposium "Bioelectrical signatures and regulators of carcinogenesis"
2013	Invited seminar speaker, Princeton University "Endogenous bioelectricity in development, regeneration, and cancer: molecular mechanisms and biomedical opportunities"
2013	Invited seminar speaker, University of Minnesota "Endogenous bioelectricity in development, regeneration, and cancer: molecular mechanisms and biomedical opportunities"
2013	Keynote speaker, NIH NCI's PS-OC meeting, Arizona "Endogenous bioelectricity in development, regeneration, and cancer: molecular mechanisms and biomedical opportunities"

International

1998	1st World Congress on Effects of Electricity and Magnetism on the Natural World, Madeira, Portugal "Endogenous electromagnetic fields as signals in development, regeneration, and neoplasm"
2001	Juan March Conference: Left-Right Asymmetry, Madrid (Won "Best Talk" award) "Role of gap junctional communication and ion transporters in early left-right patterning"
2004	Topology and Dynamics of Signalling Processes Symposium, University of Stuttgart, Hohenheim, Germany "Ion fluxes and left-right asymmetry: the large-scale biophysics of pattern formation"
2004	Institute of Anatomy and Cell Biology, University of Freiburg, Germany "Ion transporters and embryonic left-right asymmetry"
2007	Healing Foundation Centre Opening Symposium, Manchester, U.K. "Bioelectrical controls of cell behavior and regeneration"
2007	Lectures at Oxford and National Institute of Medical Research (London) in the U.K.
2008	Max Planck Institute, and Dresden Institute of Technology (2 talks) "Endogenous bioelectric controls of regeneration"
2009	Invited speaker at the Symposium (IGC Workshop) "Biophysical Mechanisms of Development", Gulbenkian Institute
2009	Invited speaker and session chair, "Mechanisms of Organ Regeneration in Model Systems" (organized by the Universidad Internacional de Andalucía)
2009	Invited talk, Centre de Biochimie Université de Nice - Faculté des Sciences
2010	Invited speaker at the International *Xenopus* conference, Banff, Canada, "Bioelectrical Techniques for Xenopus developmental biology"
2010	Invited speaker at SFB Developmental Biology conference, Freiburg, Germany "Ion flows as determinants of pattern in embryonic development and regeneration"
2010	Invited seminar speaker at EPFL, Lausanne, Switzerland "Bioelectrical controls of pattern in embryonic development and regeneration"
2010	Invited seminar speaker, IGPP Freiburg, Germany "Quantum mechanisms in mind-body interface in artificial intelligence"
2012	Keynote speaker, IFESS conference, Banff Canada, Awarded "Scientist of Vision" award
2012	Plenary speaker, 50th Anniversary IBBME symposium, Toronto, Canada
2012	Invited speaker, Gordon Conference, Italy "Transmembrane voltage gradients determine growth and form"

Service to Forsyth Institute

I have served as a member on 9 Forsyth committees, made presentations to numerous potential donors at the request of the Development office, and participated in the Summer EOP program as a mentor for 4 summers. Our work has extended the research portfolio of Forsyth into new directions (basic developmental biology of laterality-based birth defects, cancer, and regenerative medicine) and generated significant publicity for the Institute both in the popular press and in science news journals (list of media pieces on our work is available upon request). We have also expanded the funding base of Forsyth to sources other than NIDCR and NIH in general, acquiring funding from other NIH Institutes and private foundations such as AHA, MOD, TMF, ACS, and others. We have also made outreach to military funding agencies such as DOD, DARPA, etc. and established collaborations that link our work at Forsyth to top-caliber researchers all over the world.

Bridging Initiatives

I attempted to build a critical mass in cell and developmental biology at Forsyth. I founded (and served as director in) the Forsyth Center for Regenerative and Developmental Biology. We obtained seed funding and completed 1 faculty recruitment. The Center, now expanded to Tufts University, can be found at http://www.cellregeneration.org and serves as a focus for funding, collaborations, and relationships with the biotechnology industry. My goal is to leverage the discoveries made in our group by highly interdisciplinary interactions across fields and institutions.

Service to Tufts University

1. In late 2008, my lab moved to Tufts University, where I founded (and serve as Director for) The Tufts Center for Regenerative and Developmental Biology. This is an expansion of my original vision started at Forsyth, and now forms collaborations across both institutions that continue to draw the attention of students, post-docs, and the popular press. This has allowed us to move a DoD subcontract to Tufts as well initiate additional funding initiatives.
2. In 2009 I designed a course titled “Biology for Engineers” which Catherine Kuo is using in BME (ES11).
3. In 2009 I was centrally involved in writing a C06 construction proposal grant to the NIH that ultimately enabled the move of a significant portion of the department to new facilities at 200 Boston Ave.
4. Tufts Committee work:
    a. 2-4 students’ Bio193/194 committees every year
    b. 2010 – BME Faculty Search Committee
    c. 2011 - Physiology recruitment search committee, Biology Department
    d. 2012 – IGERT Applications Review Committee, Program Committee

Part III: Bibliography **(**H-index = 31 as of 2012)

Original Articles

1. Levin M. A Julia set model of field-directed morphogenesis. **Computer Applications in the Biosciences** 1994;10(2):85-103

    In this paper I developed a model of embryonic and regenerative patterning based on fractal (chaotic) dynamic behavior among gene interaction networks. The model included stochastic elements that allowed modeling of robustness.

2. Levin M, Ernst SG. AC magnetic field effects on early sea urchin development. **Bioelectromagnetics** 1995;16:231-240

    In this paper we uncovered the ability of weak magnetic fields to alter the rate of cell cycle in sea urchin embryos.

3. Levin M. Use of Genetic Algorithms to solve biomedical Problems. **M.D. Computing** 1995;12(3):193-198

   In this paper I demonstrated how to use an evolutionary programming strategy to uncover solutions to specific search problems in biology (e.g., identification of novel protein sequence domains.

4. Levin M. Discontinuous and alternate q-system fractals. **Computers and Graphics** 1994; 18(6):873-884

   In this paper I describe computer algorithms that produce fractal images in number systems where $i^2 \neq -1$.

5. Levin M. A genetic algorithm model of the evolution of animal communication. **BioSystems** 1995;36:167-178

   In this paper I show how mutual understanding and dialects of language systems arise in populations of interacting animals. I demonstrate that a significant degree of understanding can be reached by evolutionary pressure alone, requiring no prior agreement on the fixation of arbitrary symbol meanings.

6. Levin M, Johnson RL, Stern CD, Kuehn M, Tabin C. A molecular pathway determining left-right asymmetry in chick embryogenesis. **Cell** 1995;82:803-814

   This paper was significant because 1) it was the first discovery and characterization of genes which were expressed consistently-asymmetrically in embryonic development, and 2) was the first identification of a molecular pathway determining left-right asymmetry of the heart and other visceral organs. This paper identified a molecular pathway controlling the patterning of a major body axis (the left-right axis) that had never before been addressed at a molecular level. It provided the first insight into how embryos reliably orient the left-right axis, and figures from this paper now appear in all major Developmental Biology textbooks. One of the genes we identified, Nodal, was subsequently shown to be asymmetric in all vertebrates, and the elements of the pathway we identified were very informative in understanding human laterality syndromes. This work was chosen as one of the "Milestones of Developmental Biology" in the last century, by the journal Nature (see http://www.nature.com/milestones/development/milestones/) and was cited 488 times as of March 2010.

7. Levin M, Roberts D, Holmes L, Tabin C. Laterality defects in Conjoined Twins. **Nature** 1996;385:321-

   This paper was significant because it showed, for the first time, a molecular explanation for the fact that conjoined twins often exhibit laterality disturbances. This fact has been known to human medicine for a century, but had never been explained. Using the pathway we had discovered previously, we showed how cross-over of left-right signals randomizes one of the twins. Our work provided molecular insight into an important aspect of human teratology and showed how molecular investigation of chick embryos can underlie discoveries in the etiology of human birth defects.

8. Levin M, Ernst SG. DC magnetic field effects on early sea urchin development. **Bioelectromagnetics** 1997;18(3):255-263

   In this paper we show that weak static magnetic fields can disrupt the gastrulation of sea urchin development.

9. Levin M, Pagan S, Roberts D, Cooke J, Kuehn M, Tabin C. Left/Right patterning signals and the independent regulation of different aspects of situs in the chick embryo. **Developmental Biology** 1997;189:57-67

In this paper we show that Activin-□B is the earliest known asymmetric gene in chick, and that activin and Nodal control the laterality of the heart and gut in chick embryos.

10. Levin M. Follistatin mimics the endogenous streak inhibitory activity in early chick embryos. **International Journal of Developmental Biology** 1998;42:553-559

    In this paper I show that the existence of exactly one primitive streak in most chick embryos is due to competition among nascent streaks, and this competition is mediated by Follistatin system.

11. Levin M, Mercola M. Gap junctions are involved in the early generation of left right asymmetry. **Developmental Biology** 1998;203(1):90-105

    This, and paper #14, were significant because they were the first identification of the role of gap-junctional signaling in major axial patterning. We showed that small molecule signals moving through gap junctions controlled the left-right axis. These findings 1) identified a new role for the poorly-understood gap-junction signals, 2) discovered a novel mechanism in left-right patterning which was dependent not on the well-understood receptor-mediated protein signaling factors but on small molecules transferred directly through the cytoplasm, and 3) identified a left-right mechanism which functions earlier than the asymmetric gene expression which the left-right field was focused upon by this time.

12. Levin M, Mercola M. Events upstream of asymmetrical Nodal expression: reconciling the chick and frog. **Developmental Genetics** 1998;23(3):185-193

    In this paper we show address a discrepancy in asymmetric sonic hedgehog/Nodal signaling between the chick and frog systems and show that explanted tissues generate a Shh-expressing (node-like) structure de novo. Thus, we showed that counter to prior proposals, an inductive signal from the midline is indeed necessary for left-sided Nodal expression in frog.

13. Zhu L, Marvin MJ, Gardiner A, Lassar AB, Mercola M, Stern CD, Levin M. Cerberus regulates left/right asymmetry of the embryonic head and heart. **Current Biology** 1999;9(17):931-938

    In this paper we characterize a novel asymmetric gene, Cerberus, and show that it controls the asymmetry of the heart but also head.

14. Levin M, Mercola M. Gap Junction-Mediated Transfer of Left-Right Patterning Signals in the Early Chick Blastoderm is Upstream of Shh Asymmetry. **Development** 1999;126 4703-4714

    This, and paper #11, were significant because they were the first identification of the role of gap-junctional signaling in major axial patterning. We showed that physiological signals moving through gap junctions controlled the left-right axis. These findings 1) identified a new role for the poorly-understood gap-junction signals, 2) discovered a novel mechanism in left-right patterning which was dependent not on the well-understood receptor-mediated protein signaling factors but on small molecules transferred directly through the cytoplasm, and 3) identified a left-right mechanism which functions earlier than the asymmetric gene expression which the left-right field was focused upon by this time.

15. Levin M, Mercola M. Expression of Connexin30 in *Xenopus* embryos and its involvement in hatching gland function. **Developmental Dynamics** 2000;219(1):96-101

    In this paper we showed that gap junctional communication among hatching gland cells is required for secretion of hatching enzyme and subsequent embryonic hatching.

16. Levin M, Thorlin T, Robinson K, Nogi T, Mercola M., H^+/K^+-ATPase activity comprises an early step of left-right asymmetry during development. **Cell** 2002;111:77-89

*This paper showed that membrane voltage changes driven by the H,K-ATPase pump were responsible for extremely early steps in left-right patterning in both chick and frog embryos. This paper was significant because 1) it pioneered the concept of the reverse drug screen, showing that specific electrogenic gene products can be rapidly implicated in any patterning process using our strategy, 2) showed that the frog embryo aligns its left-right axis within 2 hours of fertilization, *much* earlier than previously believed in the field, 3) showed that mRNAs for ion pumps are asymmetrically localized at the 4-cell stage, indicating a completely novel aspect of mRNA localization and subcellular zipcodes, and 4) served as a proof-of-principle of how physiological and bioelectrical approaches can be merged with molecular genetics to understand biophysical, epigenetic aspects of patterning. This is an extremely important, but poorly-understood, aspect of biology. The screen we performed identified 4 targets. The first one is reported in this paper. Data on the other three represent an additional 5 papers in this series that are currently in various stages of preparation/review. Following up on our work, a number of labs have now identified similar mechanisms functioning in a wide variety of invertebrate and vertebrate organisms.*

17. Rutenberg J, Cheng SM, Levin M. Early embryonic expression of ion channels and pumps in chick and *Xenopus* embryogenesis. **Developmental Dynamics** 2002; 225(4):469-484

In this paper we analyzed expression of a number of important ion channel and pump genes and showed that early embryos exhibit a dynamic profile of ion transporter expression that can underlie very rich patterns of physiological gradients during development.

18. Cheng SM, I. Chen I, Levin M. K_{atp} channel activity is required for hatching in *Xenopus*. **Developmental Dynamics** 2002; 225(4):588-591

In this paper we show that ATP-sensitive potassium channel function is required for the function of the hatching gland in frog embryos.

19. Bunney TD, De Boer AH, Levin M. Fusicoccin signaling reveals 14-3-3 protein function as a novel step in left-right patterning during amphibian embryogenesis. **Development** 2003;130:4847-4858

This paper showed that the 14-3-3e gene product was involved in determining left-right asymmetry in very early frog embryos. This is extremely significant because the 14-3-3e protein is homologous to the PAR gene family, which is crucial to establishing cell polarity in C. elegans and Drosophila. Thus, this paper indicates a deep conservation between mechanisms establishing polarity on a cellular level in invertebrates and patterning across a major body axis in vertebrates. Such a concordance across phyla is very important for understanding the evolution of patterning control mechanisms and we here identify a gene product that serves as the first molecular entry-point to future studies to explore these fundamental mechanisms.

20. Levin M. A novel immunohistochemical method for evaluation of antibody specificity and detection of labile targets in biological tissue. **Journal of Biophysical and Biochemical Methods** 2004;58:85-96

In this paper I developed a novel method for immunohistochemical sectioning of embryonic tissue, which is also useful for characterizing antibody specificity. I also revealed that several commonly-used commercial antibodies for serotonin in fact do not distinguish between 5HT and its related metabolites.

21. Nogi T., Yuan Y., Sorocco D., Perez-Tomas R., Levin M. Eye regeneration assay reveals an invariant functional left-right asymmetry in an early bilaterian, D. japonica. **Laterality** 2005; 10(3): 193-205

    This paper demonstrated the existence of a cryptic left-right asymmetry in regeneration of the visual system of planaria – an organism that has always been considered to be left-right symmetrical.

22. Fukumoto T., Levin M. Asymmetric expression of Syndecan-2 in early chick embryogenesis. **Mechanisms of Development Gene Expression Patterns** 2005; 5: 525-528

    In this paper we showed that the Syndecan-2 gene product is asymmetrically expressed in chick embryos during gastrulation, suggesting that unlike in frog, where syndecan asymmetry appears to function at the level of phosphorylation, the chick utilizes transcriptional control.

23. Fukumoto T., Kema I., Levin M. Serotonin signaling is a very early step in patterning of the left-right axis in chick and frog embryos. **Current Biology** 2005; 15: 794-803

    This paper, and its companion paper #27, is very significant because it (1) revealed a new role for the medically important neurotransmitter serotonin, (2) showed that serotonin has functions long prior to the appearance of the embryonic nervous system, (3) characterized a novel left-right patterning mechanism (cell:cell communication via serotonin signals) functioning during cleavage stages, (4) provided evidence that the long-sought gap junction-permeant morphogen working in LR patterning is indeed serotonin, (5) suggested the existence of novel cytoplasmic receptors in addition to the known cell-membrane serotonin receptor proteins, and (6) identified a possible class of teratologies arising from commonly-used pharmaceutical drugs such as Prozac^{tm}.

24. Qiu D., Cheng S.M., Wozniak L., McSweeney M., Perrone E., Levin M. Localization and loss-of-function implicates ciliary proteins in early, cytoplasmic roles in left-right asymmetry. **Developmental Dynamics** 2005; 234: 176-189

    In this paper we provide evidence that the proteins involved in LR asymmetry assumed to be involved in ciliary function by many biologists in fact are present cytoplasmically in early frog embryos and exhibit important left-right asymmetries in both chick and frog, supporting our model of early LR determination by intracellular transport of specific proteins. We also demonstrate that, consistent with this model, actin cytoskeleton organization is functionally required for normal LR asymmetry.

25. Shin J-B., Adams D., Paukert M., Siba M., Sidi S., Levin M., Gillespie P. G., Grunder S. Xenopus TRPN1 (NOMPC) localizes to microtubule-based cilia. **P.N.A.S**. 2005; 102(35): 12572–12577

    In this paper, we show that NOMPC localizes to cilia in inner-ear hair cells of the frog embryo.

26. Gamer L. W., Nove J., Levin M., Rosen V. BMP-3 is a novel inhibitor of both activin and BMP-4 signaling in Xenopus embryos. **Developmental Biology** 2005; 285(1): 156-68

    In this paper we identify BMP-3 as a novel antagonist of both activin and BMPs and uncover how some of the diverse developmental processes that are regulated by both activin and BMP signaling can be modulated during embryogenesis.

27. Fukumoto T., Blakely R., Levin M. Serotonin transporters are a conserved, early mechanism in left-right patterning. **Developmental Neuroscience** 2005; 27(6): 349 – 363

    In this paper we demonstrate for the first time that the medically-important serotonin transporters, SERT (Prozac target) and VMAT are involved in embryonic left-

right patterning, identifying a new step in establishment of laterality and uncovering a potential source of birth defects for a common antidepressant medication.

28. Nogi T., Levin M. Characterization of innexin gene expression and functional roles of gap-junctional communication in planarian regeneration. **Developmental Biology** 2005; 287: 314 – 335

    In this paper, we clone and characterize for the first time the whole family of gap junction genes (innexins) in planaria, and show that gap junction-mediated signals are required for the proper determination of anterior-posterior polarity during regeneration.

29. Hibino T., Yuichiro I, Levin M., Nishino A. Ion flow regulates left-right asymmetry in sea urchin development. **Development**, **Genes and Evolution** 2006; 216(5): 265-76

    In papers 29 and 30, we collaborate with two invertebrate labs to show that ion flow-based LR asymmetry mechanisms that we discovered in chick and frog indeed also are conserved to invertebrates, suggesting that these physiological mechanisms are much more widely conserved throughout phyla than the proposed ciliary flow mechanisms.

30. Shimeld S. M., Levin M. Evidence for the regulation of left-right asymmetry in Ciona intestinalis by ion flux. **Developmental Dynamics** 2006; 235(6): 1543-1553

    In this paper, we demonstrate a role for ion flux in the regulation of left-right asymmetry in the sea squirt Ciona, and show a conserved, ancestral role for the H/K-ATPase ion pump in this process.

31. Adams D.S., Robinson K.R., Fukumoto T., Yuan S., Yelick P., Kuo L., McSweeney M., Levin M., Early, H^+-V-ATPase-dependent proton flux is necessary for consistent left-right patterning of non-mammalian vertebrates. **Development** 2006; 133: 1657-1671

    *In this paper, we (1) identify and characterize a new ion flow component of left-right asymmetry, the V-ATPase H^+ pump, (2) demonstrate how endogenous voltage and pH gradients can be characterized and their individual functions isolated by specific molecular reagents, (3) show that V-ATPase roles are conserved to chick, frog, and zebrafish (this is the only LR mechanism that has been explored in all three species, providing a high degree of needed information about the evolution of these mechanisms, and (4) link this mechanism to serotonergic signaling and ciliary function, providing a more complete picture of the early steps of the LR pathway in vertebrates. This paper was rated 9.0 ("exceptional") by Faculty 1000 (*http://www.f1000biology.com/article/id/1030540/evaluation#cite).

32. Hicks C., Sorocco D., Levin M. Automated Analysis of Behavior: A Computer-Controlled System for Drug Screening and the Investigation of Learning. **Journal of Neurobiology** 2006; 66(9): 977-90

    This paper presents the development of a new, automated, 2nd-generation platform for the analysis of small animal memory and behavior, and describes a dataset of novel information about planarian memory and heritability of various behavioral properties. We constructed a computer-controlled device that allows the user to individually control the environment of, and monitor, a set of animals in parallel. We have used this with planaria, zebrafish larvae, and tadpoles, to analyze behavior in organisms with a modified nervous system structure. This system enables an unlimited number of learning paradigms to be used and offers the field the ability to 1) analyze behavior in an objective way not subject to experimenter effects, 2) document all of the data in movies of each animal's chamber and Excel files, making it easy to share datasets and have primary data analyzed by other groups, 3) analyze animals in parallel allowing statistically-valid conclusions and powerful controls such as yoked, 4) allow students and other labs to interact with the behavioral experiments remotely over the internet, and 5) perform drug screens for novel

reagents with complex neuroactive properties (such as nootropic drugs that increase learning ability and memory retention). This paper is an example of our lab's application of our interdisciplinary approaches (engineering, computer science, biology, ethology) to other fields than developmental biology.

33. Esser A. T., Smith K. C., Weaver J. C., Levin M. A Mathematical Model of Morphogen Electrophoresis through Gap Junctions. **Developmental Dynamics** 2006; 235: 2144-2159

    Our prior work enabled all of the important components of early LR signaling to be determined quantitatively. This is a very unusual opportunity in developmental biology, especially as regards model systems other than Drosophila. This paper presents a mathematical/computer model of serotonin movement through gap junctions in early frog embryos; it is important because it 1) demonstrates how early physiological data can be integrated with molecular biology to construct a predictive, quantitative model of embryonic patterning, 2) shows that our previous models of gap junctional communication in LR asymmetry are physically plausible and can work using realistic quantitative measurements, 3) makes predictions which suggest new experiments for the field, and 4) illustrates the highly-interdisciplinary integrative approach of our lab to the problem of biological pattern formation.

34. Adams D. S., Levin M. Inverse Drug Screens: a rapid and inexpensive method for implicating molecular targets. **Genesis** 2006; 44: 530-540

    Here, we show how a tiered (tree-based) inverse screening approach can capitalize on the huge numbers of pharmacological reagents of differing specificity to rapidly and inexpensively identify specific gene products in any assay. The method logarithmically converges on high-value candidates and is ideal for probing roles of ion transporters, neurotransmitters, and many other pathways in novel morphogenetic contexts.

35. Tseng, A-S., Adams, D. S., Qiu, D., Koustubhan, P., Levin, M. Apoptosis is required during early stages of tail regeneration in Xenopus laevis. **Developmental Biology** 2006; 301: 62-69

    This paper shows that, surprisingly, programmed cell death of a small group of cells is required for regeneration of spinal cord and muscle. This opens the opportunity to characterize a cell population that is normally inhibitory for regeneration (and removal of which might be a useful strategy for clinical augmentation of regeneration).

36. Adams, D. S., Masi, A., and Levin, M. H^+ Pump-dependent changes in membrane voltage are an early mechanism necessary and sufficient to induce tail regeneration. **Development** 2007; 134: 1323-1335

    This paper, for the first time, identifies the specific ion transporter responsible for the unique regeneration-dependent changes in voltage gradients in regenerating tissue. We show that regeneration of spinal cord and muscle can be induced by genetic modulation of H^+ flux and transmembrane potential. This paper was selected by Science as an "Editor's Choice" and a story on this paper featured on the front page of the Nature website. It was also chosen by "Faculty of 1000 Biology". Publicity included coverage for Forsyth in the Boston Globe, New Scientist, and other media outlets.

37. Oviedo, N. J., Levin, M. Smed-inx11 is a Planarian Stem Cell Gap Junction Gene Required for Regeneration and Homeostasis", **Development** 2007; 134: 3121-3131

    This paper, for the first time, demonstrates that gap junctional communication is crucial for the information passed between adult stem cells and their niche during regeneration, and link stem cell behavior to large-scale axial pattern in the adult animal. Publicity included coverage in Nature (02 August 2007 Volume 448 Number 7153, p. 522)

38. Aw, S., Adams, D. S., Qiu, D., and Levin, M., (2007), "H,K-ATPase protein localization and Kir4.1 function reveal concordance of 3 axes during early determination of left-right asymmetry", **Mechanisms of Development**, 125: 353-372.

This paper was recommended by "Faculty of 1000 Biology" and got an award as a top-cited article for 2008-2010 from Mechanisms of Development. Here, we reveal the details of the physiological circuit which uses a potassium channel to generate transmembrane voltage gradients from the electroneutral hydrogen/potassium exchanger, and show for the first time that the early cytoskeleton in Xenopus embryos has an endogenous left-right bias that results in asymmetric distribution of molecular motor cargo.

39. Morokuma, J., Blackiston, D., and Levin, M., (2008), "KCNQ1 and KCNE1 K^+ channel components are involved in early left-right patterning in *Xenopus* embryos", **Cellular Physiology and Biochemistry**, 21: 357-372

In this paper, we implicate a new potassium channel in left-right asymmetry of frog development.

40. Morokuma, J., Blackiston, D., Adams, D. S., Trimmer, B., and Levin, M., (2008), "Modulation of K^+ channel confers a hyper-proliferative, invasive phenotype on embryonic stem cells", **PNAS**, 105(43): 16608-16613

In this paper, we show for the first time that depolarization of neighboring cells can confer a neoplastic-like phenotype upon normal melanocytes. This not only shows a novel pathway to melanoma but also illustrates a more general paradigm for how bioelectrical cues in the microenvironment can activate the stem cell → cancer cell transition and coordinate the behavior of stem cells in vivo.

41. Sundelacruz, S., M. Levin, and D. L. Kaplan, (2008), "Membrane potential controls adipogenic and osteogenic differentiation of mesenchymal stem cells", **PLoS One**, 3(11): e3737, 1-15

In this paper, we show that the differentiation state of human mesenchymal stem cells in culture can be controlled by manipulation of their transmembrane voltage potential, identifying bioelectric state as a novel and tractable control point for modulating hMSC behavior.

42. Oviedo, N. J., Nicolas, C. L., Adams, D. S., and Levin, M., (2008), "Live imaging of planarian membrane potential using DiBAC4(3)", **Cold Spring Harbor Protocols**, doi:10.1101/pdb.prot5055
43. Oviedo, N. J., Nicolas, C. L., Adams, D. S., and Levin, M., (2008), "Gene knockdown in planarians using RNA interference", **Cold Spring Harbor Protocols**, doi:10.1101/pdb.prot5054
44. Oviedo, N. J., Nicolas, C. L., Adams, D. S., and Levin, M., (2008), "Establishing and maintaining a colony of planarians", **Cold Spring Harbor Protocols**, doi:10.1101/pdb.prot5053
45. Zhang, Y., and M. Levin, (2009), "Particle tracking model of electrophoretic morphogen movement reveals stochastic dynamics of embryonic gradient", **Developmental Dynamics**, 238(8): 1923-1935

In this paper we presented a particle-tracking model of serotonin movement during early left-right patterning, uncovering some unexpected properties of the gradient's dependence on physiological state of the blastomeres and making specific quantitative predictions.

46. Zhang, Y., and M. Levin, (2009), "Left-right asymmetry in the chick embryo requires core planar cell polarity protein Vangl2, **Genesis**, 47(11): 719-728

Although a link between planar cell polarity and left-right asymmetry has been suggested, this is the first study showing that LR asymmetry is specifically dependent on PCP. Moreover, we showed this in the chick – a species which does not utilize cilia for LR asymmetry, disproving the popular model that PCP is important in left-right patterning by virtue of positioning ciliary axes.

47. N. Oviedo, J. Morokuma, P. Walentek, I. Kema, et al., M. Levin, (2010), "Long-range Neural and Gap Junction Protein-mediated Cues Control Polarity During Planarian Regeneration", **Developmental Biology**, 339: 188-199 *[Cover]*

    In this paper we show that gap-junction mediated signaling, together with CNS-mediated signals, is the basis for long-range communication enabling wounds to determine their orientation and position (required for proper regenerative polarity). Moreover, we discovered a striking phenomenon: very transient physiological modulation of GJ states is able to alter the "target morphology" of these animals, resulting in 2-headed animals that regenerate as bipolar 2-headed forms upon subsequent amputations. This reveals a novel paradigm for permanet, radical changes of body architecture and behavior by altering information resident in physiological networks (allowing, for the first time, a molecular entrypoint into the storage of an organism's "target morphology"). This change does not affect DNA, and yet is stable across the normal reproductive mode of this animal (fission+regeneration), suggesting a new type of epigenetic speciation mechanism.

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Appendix 2: List of Expert Testimony of Michael Levin, Ph.D

The following is a list of the cases wherein I testified as an expert witness at trial, hearing or by deposition.

Case:

Law firm: Robinson, Calcagnie, Robinson (Zoloft MDL)
State: New York
Deposition: 11/11/13
Trial: N/A
Case resolution: Pending

Law firm: Robinson, Calcagnie, Robinson (Zoloft MDL)
State: Philadelphia
Testified Daubert Hearing: 4/10/14
Case Resolution: Pending

Law firm: Robinson, Calcagnie, Robinson (Celexa Lexapro CA State Court)
State: Massachusetts
Deposition: 2/05/15
Trial: N/A
Case resolution: Pending

Appendix 3: References List of Michael Levin, Ph.D
I incorporate by reference my Reference List attendant to my 7/15/14 Zoloft expert report

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